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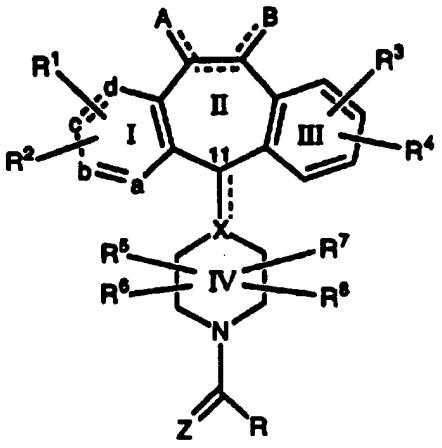
(54) Title: TRICYCLIC AMIDE AND UREA COMPOUNDS USEFUL FOR INHIBITION OF G-PROTEIN FUNCTION AND FOR TREATMENT OF PROLIFERATIVE DISEASES

(57) Abstract

A method of inhibiting Ras function and therefore inhibiting the abnormal growth of cells is disclosed. The method comprises the administration of a compound of formula (1.0) to a biological system. In particular, the method inhibits the abnormal growth of cells in a mammal such as a human being. Novel compounds wherein X is N, C or OH and R is (I) or (II) are disclosed.



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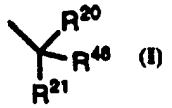

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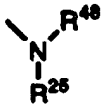

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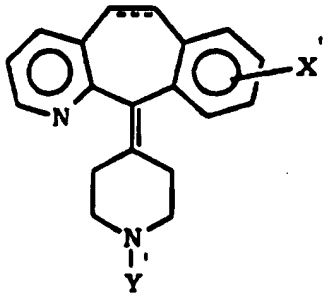
TRICYCLIC AMIDE AND UREA COMPOUNDS USEFUL FOR INHIBITION OF G-PROTEIN FUNCTION AND FOR TREATMENT OF PROLIFERATIVE DISEASES

BACKGROUND

International Publication Number WO92/11034, published July 9, 1992, discloses a method of increasing the sensitivity of a tumor to an antineoplastic agent, which tumor is resistant to the antineoplastic agent, by the concurrent administration of the antineoplastic agent and a potentiating agent of the formula:



wherein Y' is hydrogen, substituted carboxylate or substituted sulfonyl. Examples of such potentiating agents include 11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridines such as Loratadine.

To acquire transforming potential, the precursor of the Ras oncoprotein must undergo farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, have therefore been suggested as anticancer agents for tumors in which Ras contributes to transformation. Mutated, oncogenic forms of ras are frequently found in many human cancers, most notably in more than 50% of colon and pancreatic carcinomas (Kohl et al., Science, Vol. 260, 1834 to 1837, 1993).

A welcome contribution to the art would be compounds useful for the inhibition of farnesyl protein transferase. Such a contribution is provided by this invention.

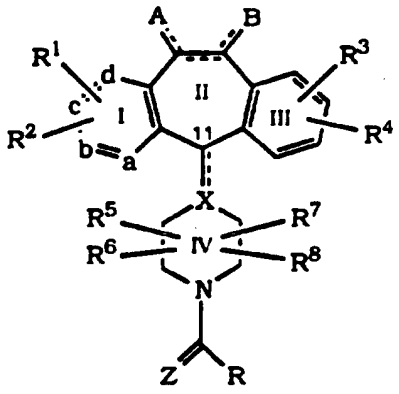
SUMMARY OF THE INVENTION

Inhibition of farnesyl protein transferase by tricyclic compounds of this invention has not been reported previously. Thus, this invention provides a method for inhibiting farnesyl protein transferase using tricyclic

compounds of this invention which: (i) potently inhibit farnesyl protein transferase, but not geranylgeranyl protein transferase I, in vitro; (ii) block the phenotypic change induced by a form of transforming Ras which is a farnesyl acceptor but not by a form of transforming Ras engineered to be a geranylgeranyl acceptor; (iii) block intracellular processing of Ras which is a farnesyl acceptor but not of Ras engineered to be a geranylgeranyl acceptor; and (iv) block abnormal cell growth in culture induced by transforming Ras. Several compounds of this invention have been demonstrated to have anti-tumor activity in animal models.

This invention provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of this invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; and (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

Compounds useful in the claimed methods are represented by Formula 1.0:



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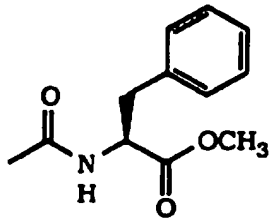
or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N or NR^9 wherein R^9 is O^-, $-CH_3$ or $-(CH_2)_nCO_2H$ wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR^1 or CR^2; or

each of a, b, c, and d are independently selected from CR^1 or CR^2;

each R^1 and each R^2 is independently selected from H, halo, $-CF_3$, $-OR^{10}$ (e.g., $-OCH_3$), $-COR^{10}$, $-SR^{10}$ (e.g., $-SCH_3$ and $-SCH_2C_6H_5$), $-S(O)_tR^{11}$ (wherein t is 0, 1 or 2, e.g., $-SOCH_3$ and $-SO_2CH_3$), -SCN, $-N(R^{10})_2$, $-NR^{10}R^{11}$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, -CN,

$-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-CONHR^{10}$, $-CONHCH_2CH_2OH$, $-NR^{10}COOR^{11}$,



$-SR^{11}C(O)OR^{11}$ (e.g., $-SCH_2CO_2CH_3$), $-SR^{11}N(R^{75})_2$ wherein each R^{75} is independently selected from H and $-C(O)OR^{11}$ (e.g., $-S(CH_2)_2NHC(O)O$-t-butyl and $-S(CH_2)_2NH_2$), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio (e.g., alkyl substituted tetrazol5-ylthio such as 1-methyl-tetrazol-5-ylthio), alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, $-OR^{10}$ or $-CO_2R^{10}$;

R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2, or R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring (Ring III);

R^5, R^6, R^7 and R^8 each independently represents H, $-CF_3$, $-COR^{10}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-OR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$, $-NR^{10}COOR^{11}$, $-N(R^{10})_2$, $-NO_2$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{11}$, $-CO_2R^{10}$, OPO_3R^{10} or one of R^5, R^6, R^7 and R^8 can be taken in combination with R^{40} as defined below to represent $-(CH_2)_r-$ wherein r is 1 to 4 which can be substituted with lower alkyl, lower alkoxy, $-CF_3$ or aryl, or R^5 is combined with R^6 to represent =O or =S and/or R^7 is combined with R^8 to represent =O or =S;

R^{10} represents H, alkyl, aryl, or aralkyl (e.g., benzyl);

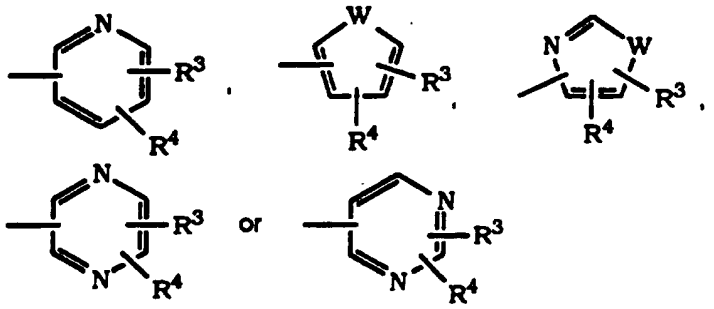
R^{11} represents alkyl or aryl;

X represents N, CH or C, which C may contain an optional double bond (represented by the dotted line) to carbon atom 11;

the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent $-NO_2$, $-R^{10}$, halo, $-OR^{11}$, $-OCO_2R^{11}$ or $-OC(O)R^{10}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2, $-(OR^{11})_2$, H and halo, dihalo, alkyl and H, $(alkyl)_2$, -H and $-OC(O)R^{10}$, H and $-OR^{10}$, =O, aryl and H, $=NOR^{10}$ or $-O-(CH_2)_p-O-$ wherein p is 2, 3 or 4;

R represents R^{40}, R^{42}, R^{44}, or R^{54}, as defined below;

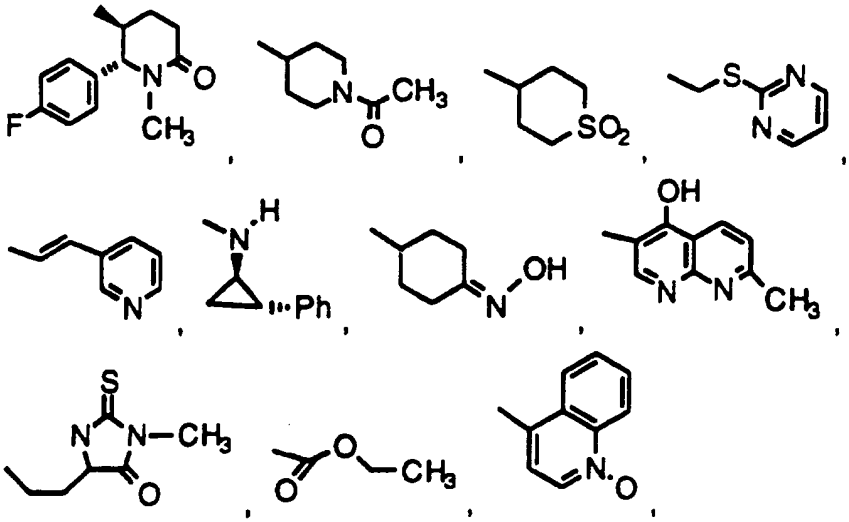
R^{40} represents H, aryl, alkyl, cycloalkyl, alkenyl, alkynyl or -D wherein -D represents

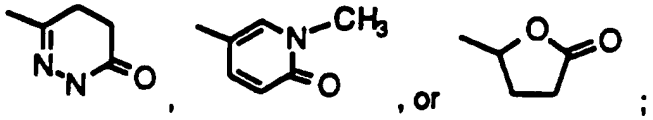


wherein R^3 and R^4 are as previously defined and W is O, S or NR^{10} wherein R^{10} is as defined above; said R^{40} cycloalkyl, alkenyl and alkynyl groups being optionally substituted with from 1-3 groups selected from halo, $-CON(R^{10})_2$, aryl, $-CO_2R^{10}$, $-OR^{12}$, $-SR^{12}$, $-N(R^{10})_2$, $-N(R^{10})CO_2R^{11}$, $-COR^{12}$, $-NO_2$ or D, wherein -D, R^{10} and R^{11} are as defined above and R^{12} represents R^{10}, $-(CH_2)_mOR^{10}$ or $-(CH_2)_qCO_2R^{10}$ wherein R^{10} is as previously defined, m is 1 to 4 and q is 0 to 4; said alkenyl and alkynyl R^{40} groups not containing -OH, -SH or $-N(R^{10})_2$ on a carbon containing a double or triple bond respectively; or

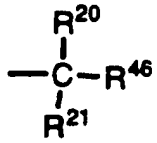
R^{40} represents phenyl substituted with a group selected from $-SO_2NH_2$, $-NHSO_2CH_3$, $-SO_2NHCH_3$, $-SO_2CH_3$, $-SOCH_3$, $-SCH_3$, or $-NHSO_2CF_3$, preferably, said group is located in the para (p-) position of the phenyl ring; or

R^{40} represents a group selected from





R^{42} represents



wherein R^{20}, R^{21} and R^{46} are each independently selected from the group consisting of:

(1) H;

(2) $-(CH_2)_qSC(O)CH_3$ wherein q is 1 to 3 (e.g., $-CH_2SC(O)CH_3$);

(3) $-(CH_2)_qOSO_2CH_3$ wherein q is 1 to 3 (e.g., $-CH_2OSO_2CH_3$);

(4) -OH;

(5) $-CS(CH_2)_w$(substituted phenyl) wherein w is 1 to 3 and the substitutents on said substituted phenyl group are the same substitutents as described below for said substituted phenyl (e.g., -C-S-CH_2-4-methoxyphenyl);

(6) $-NH_2$;

(7) -NHCBZ (wherein CBZ stands for carbonylbenzyloxy--i.e., CBZ represents $-C(O)OCH_2C_6H_5$);

(8) $-NHC(O)OR^{22}$ wherein R^{22} is an alkyl group having from 1 to 5 carbon atoms (e.g., R^{22} is t-butyl thus forming -NHBOC wherein BOC stands for tert-butyloxycarbonyl--i.e., BOC represents $-C(O)OC(CH_3)_3$), or R^{22} represents phenyl substituted with 1 to 3 alkyl groups (e.g., 4-methylphenyl);

(9) alkyl (e.g., ethyl);

(10) $-(CH_2)_k$phenyl wherein k is 1 to 6, usually 1 to 4 and preferably 1 (e.g., benzyl);

(11) phenyl;

(12) substituted phenyl (i.e., phenyl substituted with from 1 to 3 substituents, preferably one) wherein the substituents are selected from the group consisting of: halo (e.g., Br, Cl, or I, with Br being preferred); NO_2; -OH; $-OCH_3$; $-NH_2$; $-NHR^{22}$; $-N(R^{22})_2$; alkyl (e.g., alkyl having from 1 to 3 carbons with methyl being preferred); $-O(CH_2)_t$phenyl (wherein t is from 1 to 3 with 1 being preferred); and $-O(CH_2)_t$substituted phenyl (wherein t is from 1 to 3 with 1 being preferred); examples of substituted phenyls include, but are not limited to, p-bromophenyl, m-nitrophenyl, o-

nitrophenyl, m-hydroxyphenyl, o-hydroxyphenyl, methoxyphenyl, p-methylphenyl, m-methylphenyl, and -$OCH_2C_6H_5$;

(13) naphthyl;

(14) substituted naphthyl, wherein the substituents are as defined for substituted phenyl above;

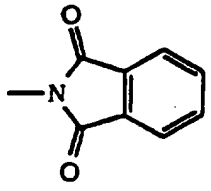
(15) bridged polycyclic hydrocarbons having from 5 to 10 carbon atoms (e.g., adamantyl and norbornyl);

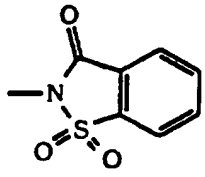
(16) cycloalkyl having from 5 to 7 carbon atoms (e.g., cyclopentyl, and cyclohexyl);

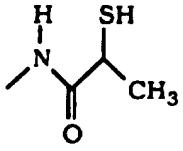
(17) heteroaryl (e.g., pyridyl, and pyridyl N-oxide);

(18) hydroxyalkyl (e.g., -$(CH_2)_vOH$ wherein v is 1 to 3, such as, for example, -CH_2OH);

(19) substituted pyridyl or substituted pyridyl N-oxide wherein the substituents are selected from methylpyridyl, morpholinyl, imidazolyl, 1-piperidinyl, 1-(4-methylpiperazinyl), -$S(O)_tR^{11}$, or any of the substituents given above for said substituted phenyl, and said substitutents are bound to a ring carbon by replacement of the hydrogen bound to said carbon;

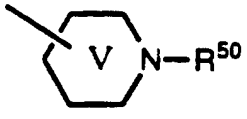
(20)  ;

(21)  ;

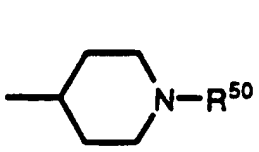
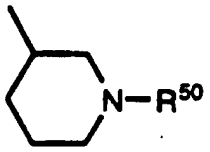
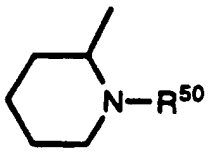
(22)  ;

(23) -$NHC(O)$-$(CH_2)_k$-phenyl or -$NH(O)$-$(CH_2)_k$-substitued phenyl, wherein said k is as defined above (i.e., 1-6, usually 1-4 and preferably 1);

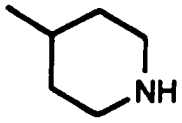
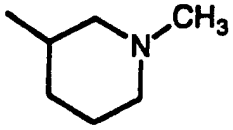
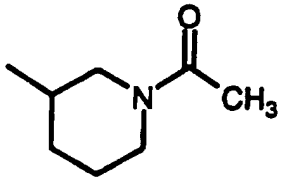
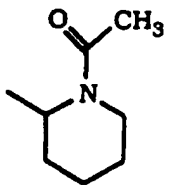
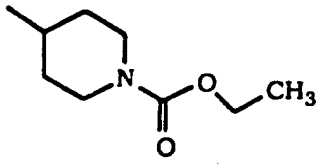
(24) piperidine Ring V:



wherein R^{50} represents H, alkyl (e.g., methyl), alkylcarbonyl (e.g., $CH_3C(O)$-), alkyloxycarbonyl (e.g., -$C(O)O$-t-C_4H_9, -$C(O)OC_2H_5$, and -$C(O)OCH_3$), haloalkyl (e.g., trifluromethyl), or --$C(O)NH(R^{10})$ wherein R^{10} is H or alkyl; Ring V includes




, and ;

examples of Ring V include: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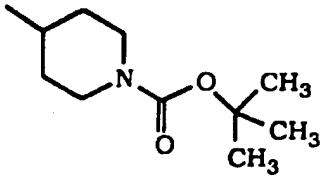
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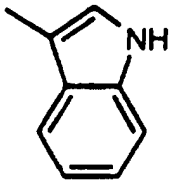
(25) -NHC(O)$CH_2C_6H_5$ or -NHC(O)CH_2-substituted-C_6H_5, for example -NHC(O)CH_2-p-hydroxyphenyl, -NHC(O)CH_2-m-hydroxyphenyl, and -NHC(O)CH_2-o-hydroxyphenyl;

(26) -NHC(O)OC_6H_5;

(27) (28) (29)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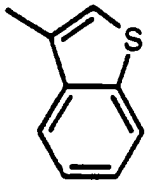
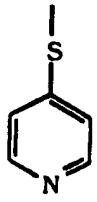
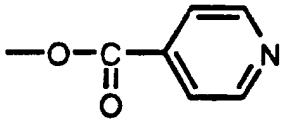

;

;

(30) -OC(O)-heteroaryl, for example

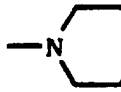
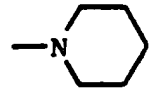
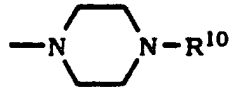
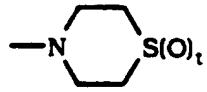

;

(31) -O-alkyl (e.g., -OCH_3);

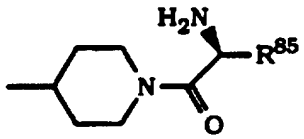
(32) -CF_3;

(33) -CN;

(34) a heterocycloalkyl group of the formula




, or

;

(35) a piperidinyl group of the formula

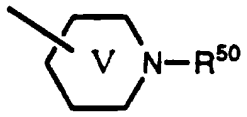


wherein R^{85} is H, alkyl, or alkyl substituted by -OH, $-SCH_3$ or -SH (preferably -OH or $-SCH_3$); and

(36) triazolyl; or

R^{20} and R^{21} taken together form a =O group and the remaining R^{46} is as defined above; or

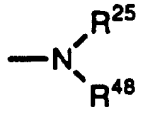
two of R^{20}, R^{21} and R^{46} taken together form piperidine Ring V



wherein Ring V and R^{50} are as defined above;

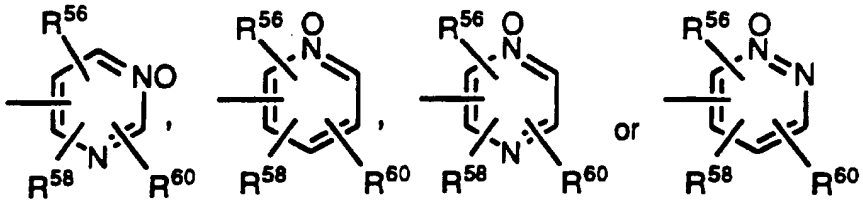
with the proviso R^{46}, R^{20}, and R^{21} are selected such that the carbon atom to which they are bound does not contain more than one heteroatom (i.e., R^{46}, R^{20}, and R^{21} are selected such that the carbon atom to which they are bound contains 0 or 1 heteroatom);

R^{44} represents



wherein R^{25} represents heteroaryl (e.g., pyridyl or pyridyl N-oxide), N-methylpiperidinyl or aryl (e.g., phenyl and substituted phenyl); and R^{48} represents H or alkyl (e.g., methyl);

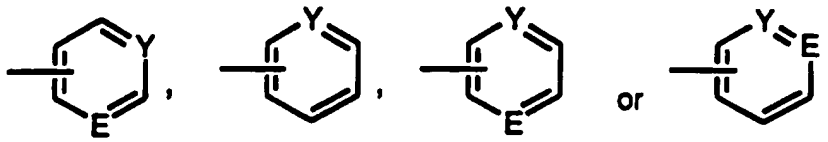
R^{54} represents an N-oxide heterocyclic group of the formula (i), (ii), (iii) or (iv):



(i) (ii) (iii) (iv)

wherein R^{56}, R^{58}, and R^{60} are the same or different and each is independently selected from H, halo, $-CF_3$, $-OR^{10}$, $-C(O)R^{10}$, $-SR^{10}$, $-S(O)_eR^{11}$ (wherein e is 1 or 2), $-N(R^{10})_2$, $-NO_2$, $-CO_2R^{10}$, $-OCO_2R^{11}$, $-OCOR^{10}$, alkyl, aryl, alkenyl or alkynyl, which alkyl may be substituted with $-OR^{10}$, $-SR^{10}$ or $-N(R^{10})_2$ and which alkenyl may be substituted with OR^{11} or SR^{11}; or

R^{54} represents an N-oxide heterocyclic group of the formula (ia), (iia), (iiia) or (iva):



(ia) (iia) (iiia) (iva)

wherein Y represents N^+-O^- and E represents N; or

R^{54} represents an alkyl group substituted with one of said N-oxide heterocyclic groups (i), (ii), (iii), (iv), (ia), (iia), (iiia) or (iva);

Z represents O or S such that R can be taken in combination with R^5, R^6, R^7 or R^8 as defined above, or R represents R^{40}, R^{42}, R^{44} or R^{54};

with the proviso that when:

(1) R^1, R^2, R^3 and R^4 are independently selected from H, halo, $-CF_3$, $-OR^{10}$, $-COR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$, $-N(R^{10})_2$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, -CN, $-NR^{10}COOR^{11}$, $-SR^{11}C(O)OR^{11}$, $-SR^{11}N(R^{75})_2$, benzotriazol-1-yloxy, tetrazol-5-ylthio, substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl; or R^1 and R^2 are selected from H, halo, $-CF_3$, $-OR^{10}$, $-COR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$, $-N(R^{10})_2$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, -CN, $-NR^{10}COOR^{11}$, $-SR^{11}C(O)OR^{11}$, $-SR^{11}N(R^{75})_2$, benzotriazol-1-yloxy, tetrazol-5-ylthio, substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl, and R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring (Ring III); and

(2) the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent $-R^{10}$, halo, $-OR^{11}$, $-OCO_2R^{11}$ or $-OC(O)R^{10}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2, $-(OR^{11})_2$, H and halo, dihalo, alkyl and H, $(alkyl)_2$, -H and $-OC(O)R^{10}$, H and $-OR^{10}$, =O, aryl and H, $=NOR^{10}$ or $-O-(CH_2)_p-O-$ wherein p is 2, 3 or 4;

then R is selected from:

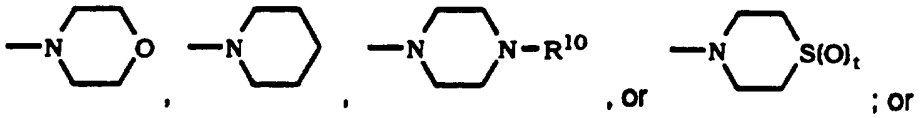
(a) R^{42} wherein at least one of R^{20}, R^{21} or R^{46} is selected from:

(1) substituted pyridyl or substituted pyridyl N-oxide wherein the substituents are selected from methylpyridyl, morpholinyl, imidazolyl, 1-piperidinyl, 1-(4-methylpiperazinyl), or $-S(O)_tR^{11}$;

(2) -CN;

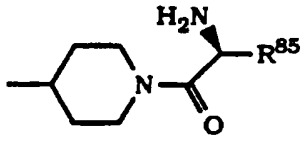
(3) triazolyl;

(4) a heterocycloalkyl group of the formula



; or

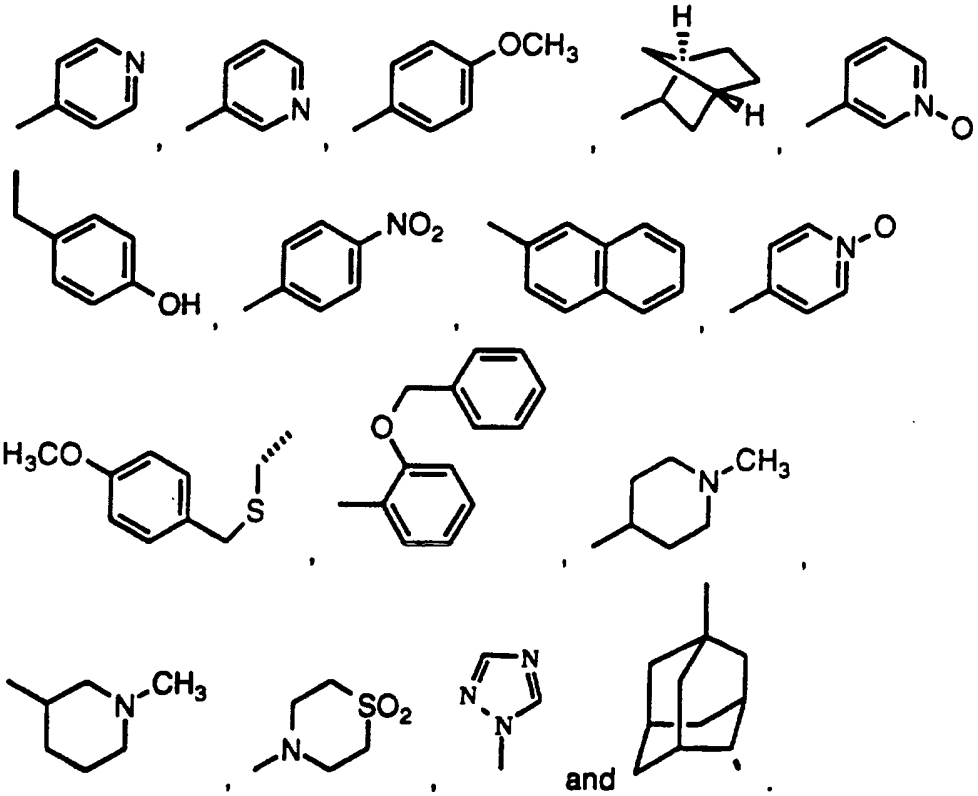
(5) a piperidinyl group of the formula



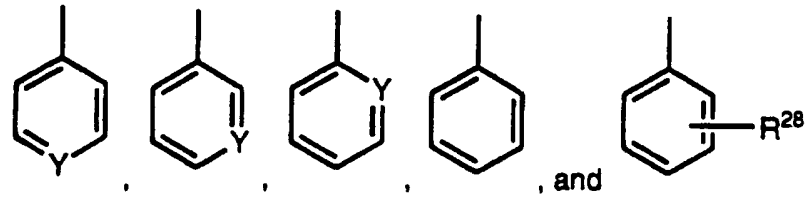
wherein R^{85} is H, alkyl, or alkyl substituted by -OH, $-SCH_3$ or -SH (preferably -OH or $-SCH_3$); or

(b) R^{44} wherein R^{25} is N-methylpiperidinyl.

Examples of R^{20}, R^{21}, and R^{46} for the above formulas include:

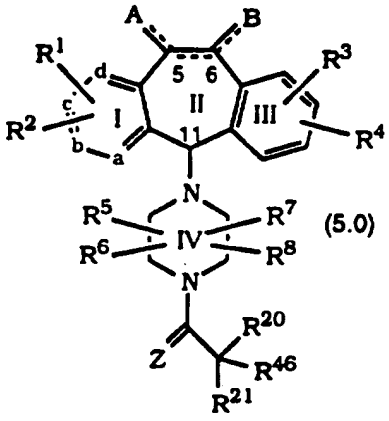


Examples of R^{25} groups include:

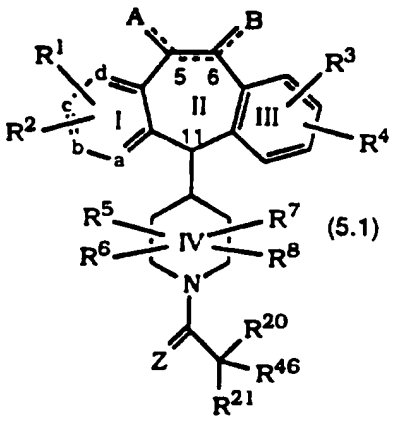


wherein Y represents N or NO, R^{28} is selected from the group consisting of: C_1 to C_4 alkyl, halo, hydroxy, NO_2, amino ($-NH_2$), $-NHR^{30}$, and $-N(R^{30})_2$ wherein R^{30} represents C_1 to C_6 alkyl.

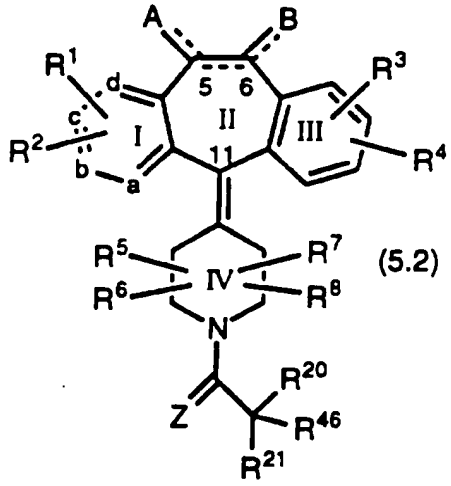
This invention also provides novel compounds of Formula 1.0 having the Formula 5.0. This invention further provides novel compounds of Formula 1.0 having the Formula 5.1. Additionally, this invention provides novel compounds of Formula 1.0 having the Formula 5.2. These formulas are identified below and all substituents are as defined for Formula 1.0:



(5.0)

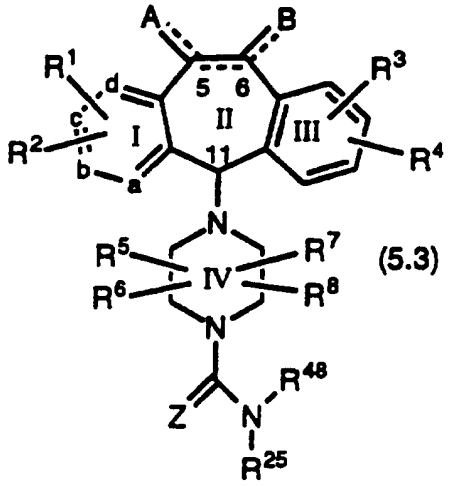


(5.1)

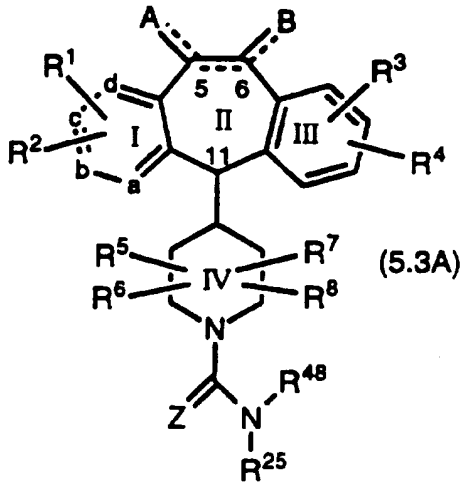


(5.2)

This invention further provides novel compounds of Formula 1.0 having the formula:

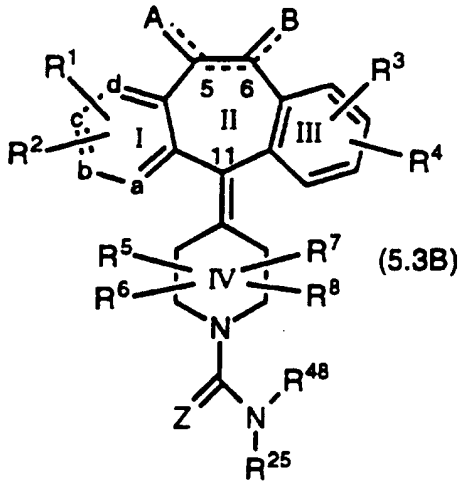


(5.3)



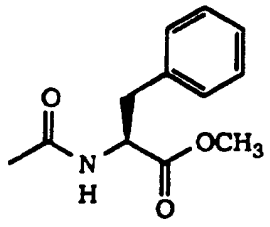
(5.3A)

or



(5.3B)

wherein a, b, c, d, R^5, R^6, R^7, R^8, A, B and Z are as defined for Formula (5.0; each R^1 and each R^2 is independently selected from H, halo, $-CF_3$, $-OR^{10}$, $-COR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$ (wherein t is 0, 1 or 2), -SCN, $-N(R^{10})_2$, $-NR^{10}R^{11}$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, -CN, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-CONHR^{10}$, $-CONHCH_2CH_2OH$, $-NR^{10}COOR^{11}$, $-SR^{11}C(O)OR^{11}$,

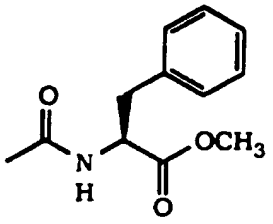


$-SR^{11}N(R^{75})_2$ (wherein each R^{75} is independently selected from H and $-C(O)OR^{11}$), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally

being substituted with halo, -OR^{10} or -CO_2R^{10}; R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2, or R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring; R^{25} represents heteroaryl, N-methylpiperdinyl or aryl (preferably R^{25} represents heteroaryl); and R^{48} represents H or alkyl; and

with the proviso that:

(1) when R^{25} is selected from heteroaryl or aryl then: (a) at least one of said R^1, R^2, R^3 and R^4 groups is selected from -SCN, -$NR^{10}R^{11}$, -$NHC(O)R^{10}$, -$NHSO_2R^{10}$, -$CONHR^{10}$, -$CONHCH_2CH_2OH$, or



; or

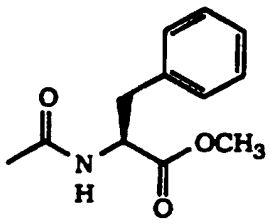
(b) the double bond between carbon atoms 5 and 6 is present and at least one of A and B represents -NO_2; and

(2) when R^{25} is N-methylpiperidinyl selected from 3-N-methyl-piperidinyl or 4-N-methylpiperidinyl then R^1 and R^2 are not H, halo, -CF_3, benzotriazol-1yloxy or lower alkyl when: (a) R^3 and R^4 are selected from H and halo; and (b) the double bond between carbon atoms 5 and 6 is present and A and B are selected from H, lower alkyl or lower alkoxy, or the double bond between carbon atoms 5 and 6 is absent and A and B are selected from H_2, (-H and -OH) or =O; and (c) R^5, R^6, R^7, and R^8 are H; and (d) Z is O.

Compounds of 5.3, 5.3A and 5.3B also include compounds wherein when R^{25} is N-methylpiperidinyl selected from 3-N-methyl-piperidinyl or 4-N-methylpiperidinyl then R^1 and R^2 are not H, halo, -CF_3, benzotriazol-1yloxy or lower alkyl.

Compounds of 5.3, 5.3A and 5.3B further include compounds wherein when R^{25} is N-methylpiperidinyl then R^1 and R^2 are not H, halo, -CF_3, benzotriazol-1yloxy or lower alkyl.

Compounds of 5.3, 5.3A and 5.3B also include compounds wherein when R^{25} is N-methylpiperidinyl then: (1) at least one of said R^1, R^2, R^3 and R^4 is selected from: -SCN, -$NR^{10}R^{11}$, -$NHC(O)R^{10}$, -$NHSO_2R^{10}$, -$CONHR^{10}$, -$CONHCH_2CH_2OH$, or



; or

(2) the double bond between carbon atoms 5 and 6 is present and at least one of A and B represents $-NO_2$.

This invention also provides a method for inhibiting tumor growth by administering an effective amount of the tricyclic compounds, described herein, to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a method for inhibiting the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount of the above described compounds. Examples of tumors which may be inhibited include, but are not limited to, lung cancer (e.g., lung adenocarcinoma), pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), bladder carcinoma and epidermal carcinoma.

It is believed that this invention also provides a method for inhibiting proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes--i.e., the Ras gene itself is not activated by mutation to an oncogenic form--with said inhibition being accomplished by the administration of an effective amount of the tricyclic compounds described herein, to a mammal (e.g., a human) in need of such treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, and fyn), may be inhibited by the tricyclic compounds described herein.

The compounds of this invention inhibit farnesyl protein transferase and the farnesylation of the oncogene protein Ras. This invention further provides a method of inhibiting ras farnesyl protein transferase, in mammals, especially humans, by the administration of an effective amount of the tricyclic compounds described above. The administration of the

compounds of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers described above.

The tricyclic compounds useful in the methods of this invention inhibit the abnormal growth of cells. Without wishing to be bound by theory, it is believed that these compounds may function through the inhibition of G-protein function, such as ras p21, by blocking G-protein isoprenylation, thus making them useful in the treatment of proliferative diseases such as tumor growth and cancer. Without wishing to be bound by theory, it is believed that these compounds inhibit ras farnesyl protein transferase, and thus show antiproliferative activity against ras transformed cells.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the following terms are used as defined below unless otherwise indicated:

MH^+-represents the molecular ion plus hydrogen of the molecule in the mass spectrum;

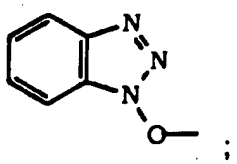
Bu-represents butyl;

Et-represents ethyl;

Me-represents methyl;

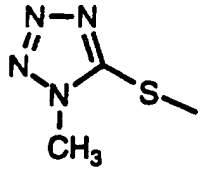
Ph-represents phenyl;

benzotriazol-1-yloxy represents



;

1-methyl-tetrazol-5-ylthio represents



;

alkyl-(including the alkyl portions of alkoxy, alkylamino and dialkylamino)-represents straight and branched carbon chains and contains from one to twenty carbon atoms, preferably one to six carbon atoms;

alkanediyl-represents a divalent, straight or branched hydrocarbon chain having from 1 to 20 carbon atoms, preferably 1 to 6 carbon atoms, the two available bonds being from the same or different carbon atoms thereof, e.g., methylene, ethylene, ethylidene,

$-CH_2CH_2CH_2-$, $-CH_2CHCH_3$, $-CHCH_2CH_3$, etc.

cycloalkyl-represents saturated carbocyclic rings branched or unbranched of from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms;

heterocycloalkyl-represents a saturated, branched or unbranched carbocylic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 hetero groups selected from -O-, -S- or - NR^{10}-(suitable heterocycloalkyl groups including 2- or 3-tetrahydrofuranyl, 2- or 3- tetrahydrothienyl, 2-, 3- or 4-piperidinyl, 2- or 3-pyrrolidinyl, 2- or 3-piperizinyl, 2- or 4-dioxanyl, etc.);

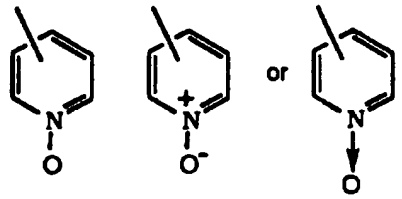
alkenyl-represents straight and branched carbon chains having at least one carbon to carbon double bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms and most preferably from 3 to 6 carbon atoms;

alkynyl-represents straight and branched carbon chains having at least one carbon to carbon triple bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms;

aryl (including the aryl portion of aryloxy and aralkyl)-represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is a phenyl ring), with all available substitutable carbon atoms of the carbocyclic group being intended as possible points of attachment, said carbocyclic group being optionally substituted (e.g., 1 to 3) with one or more of halo, alkyl, hydroxy, alkoxy, phenoxy, CF_3, amino, alkylamino, dialkylamino, $-COOR^{10}$ or $-NO_2$; and

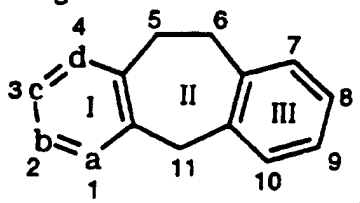
halo-represents fluoro, chloro, bromo and iodo; and

heteroaryl-represents cyclic groups, optionally substituted with R^3 and R^4, having at least one heteroatom selected from O, S or N, said heteroatom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups preferably containing from 2 to 14 carbon atoms, e.g., triazolyl, 2-, 3- or 4-pyridyl or pyridyl N-oxide (optionally substituted with R^3 and R^4), wherein pyridyl N-oxide can be represented as:



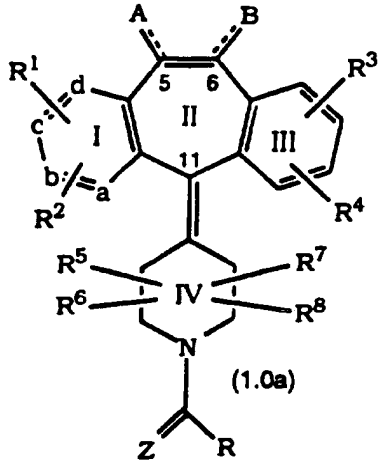
The following solvents and reagents are referred to herein by the abbreviations indicated: tetrahydrofuran (THF); ethanol (EtOH); methanol (MeOH); acetic acid (HOAc or AcOH); ethyl acetate (EtOAc); N,N-dimethylformamide (DMF); trifluoroacetic acid (TFA); trifluoroacetic anhydride (TFAA); 1-hydroxybenzotriazole (HOBT); m-chloroperbenzoic acid (MCPBA); triethylamine (Et_3N); diethyl ether (Et_2O); ethyl chloroformate ($ClCO_2Et$); and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (DEC).

Reference to the position of the substituents R^1, R^2, R^3, and R^4 is based on the numbered ring structure:

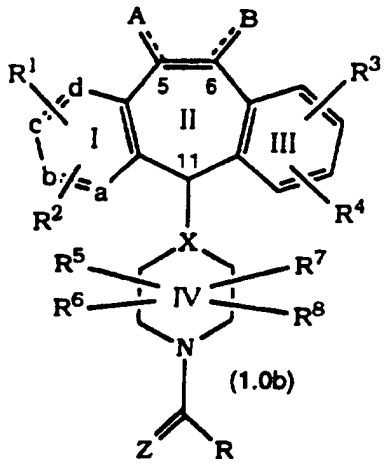


For example, R^1 can be at the C-4 position and R^2 can be at the C-2 or C-3 position. Also, for example, R^3 can be at the C-8 position and R^4 can be at the C-9 position.

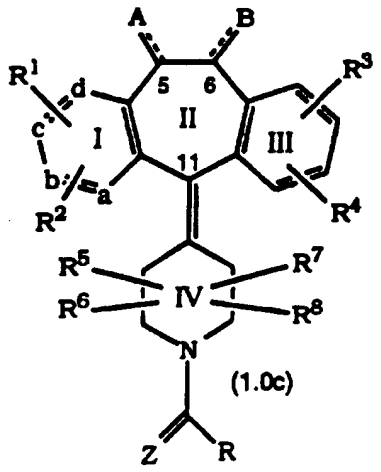
Representative structures of Formula 1.0 include but are not limited to:



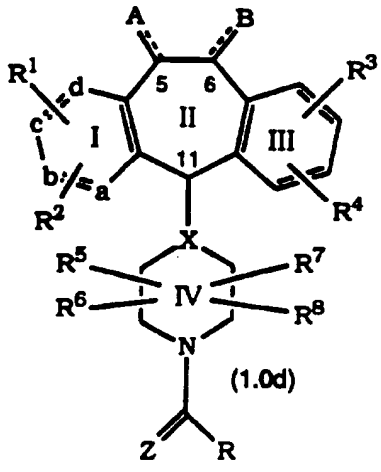
(1.0a)



(1.0b)



and



Preferably, for the compounds of Formula 1.0 (including 1.0a to 1.0d):

each of a, b, c, and d are C (carbon); or

one of a, b, c and d (most preferably a) represents N or NO, most preferably N, and the remaining a, b, c and d groups represent CR^1 or CR^2;

each R^1 and each R^2 is independently selected from H, halo (e.g., Cl, Br and F), $-CF_3$, $-OR^{10}$ (e.g., hydroxy and alkoxy (e.g., $-OCH_3$)), alkyl (e.g., methyl and t-butyl, said alkyl group being optionally substituted with halo), benzotriazol-1-yloxy, $-S(O)_tR^{11}$ (e.g., $-SCH_2CH_3$), $-SR^{11}C(O)OR^{11}$ (e.g., $-SCH_2CO_2CH_3$), $-SR^{10}$ (e.g., R^{10} represents $-CH_2C_6H_5$) and 1-methyl-tetrazol-5-ylthio; most preferably R^1 and R^2 are independently H, halo, $-CF_3$, lower alkyl (e.g., C_1 to C_4, more preferably methyl) or benzotriazol-1-yloxy; more preferably R^1 is Cl or H, and R^2 is H, Cl or Br; still more preferably R^1 is at the C-4 position, and R^2 is at the C-3 position; even more preferably R^2 is Br, Cl or I;

R^3 and R^4 are the same or different and each independently represents H, halo, $-CF_3$, $-OR^{10}$, $-COR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$ (wherein t is 0, 1 or 2), $-N(R^{10})_2$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, $-C(O)NHR^{10}$, $-CN$, $-NR^{10}COOR^{11}$, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, $-OR^{10}$ or $-CO_2R^{10}$; most preferably R^3 and R^4 independently represent H, halo, $-CF_3$, $-OR^{10}$ or alkyl (said alkyl group being optionally substituted with halo); more preferably R^3 and R^4 independently represent H or halo (e.g., Cl, Br, or F); even more preferably R^3 is at the C-8 position and R^4 is at the C-9 positon; still more preferably R^3 is Cl at the C-8 position and R^4 is H at the C-9 position;

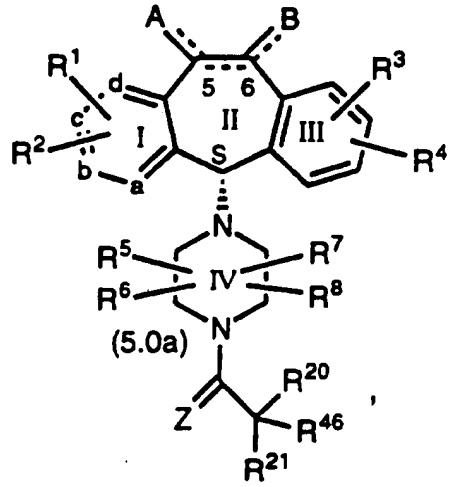
R^5, R^6, R^7 and R^8 each independently represents H, $-CF_3$ or alkyl (said alkyl optionally being substituted with $-OR^{10}$); most preferably R^5, R^6, R^7 and R^8 independently represent H and alkyl, and more preferably H;

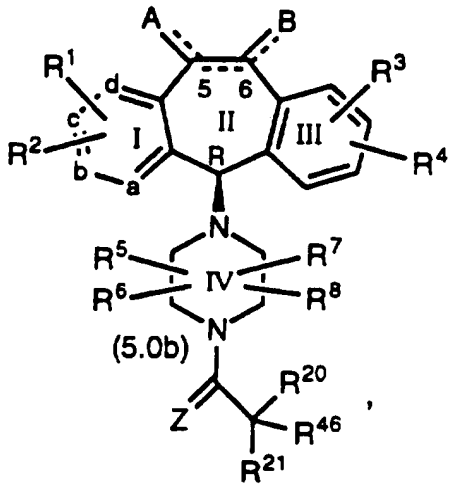
when the optional double bond between carbon atoms 5 and 6 is present, A and B independently represent H, $-R^{10}$ or $-OR^{10}$, most preferably H, lower alkyl (C_1 to C_4) and alkyloxy (i.e., R^{10} represents alkyl), more preferably H and -OH, and still more preferably H; and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2, $-(OR^{10})_2$, alkyl and H, $(alkyl)_2$, - H and $-OR^{10}$ or =O, most preferably H_2, -H and -OH, or =O, and more preferably A represents H_2 and B represents H_2 or =O;

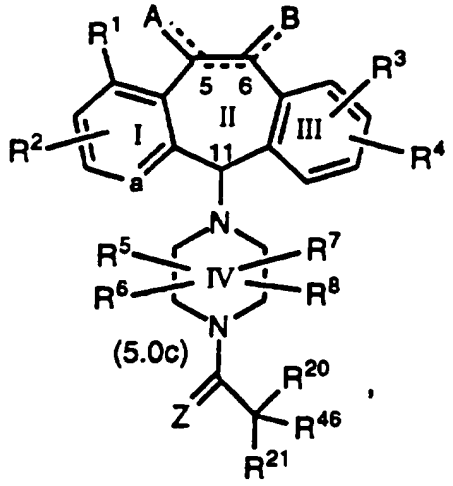
R represents R^{42} or R^{44}; and

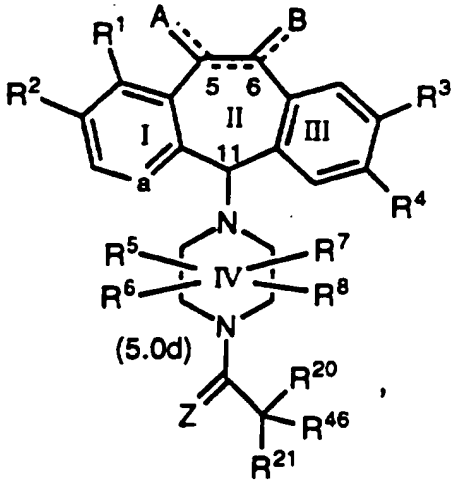
Z represents O or S, and most preferably O.

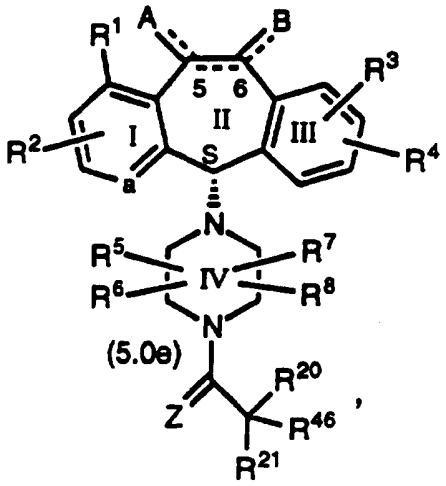
Compounds of Formula 5.0 include:



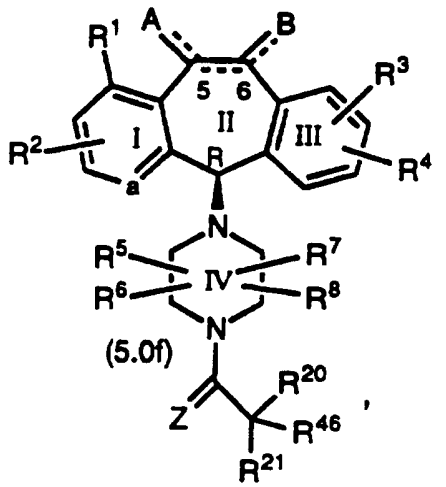




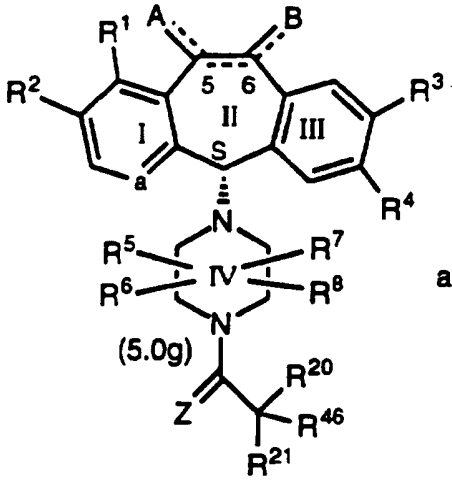




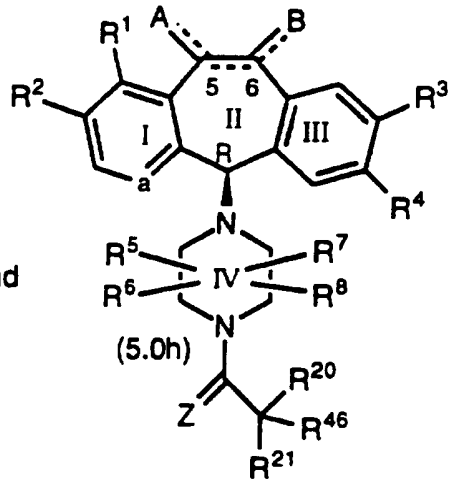
(5.0e),



(5.0f),

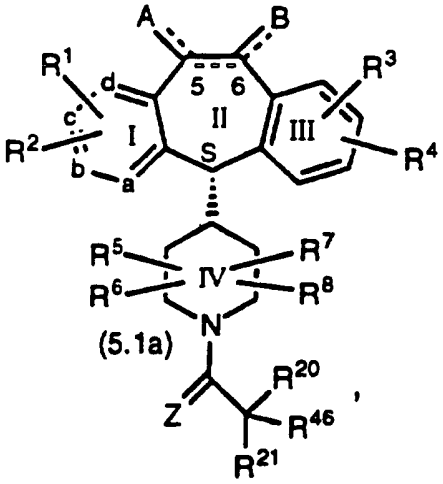


(5.0g) and

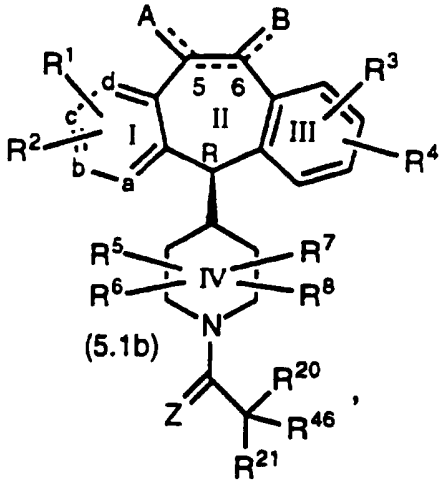


(5.0h)

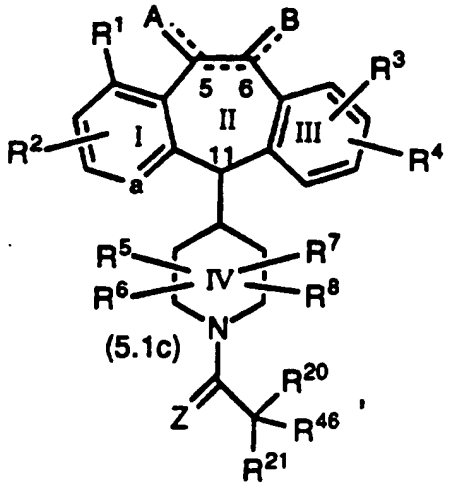
Compounds of Formula 5.1 include:



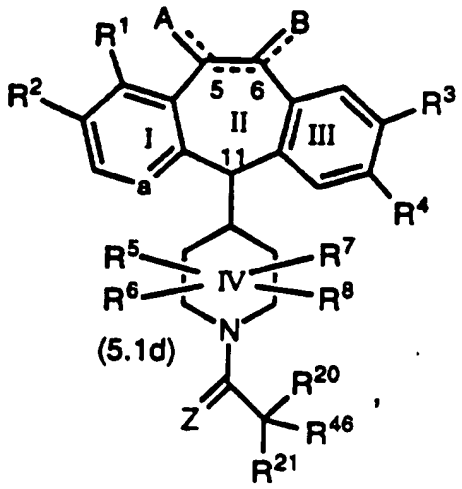
(5.1a),



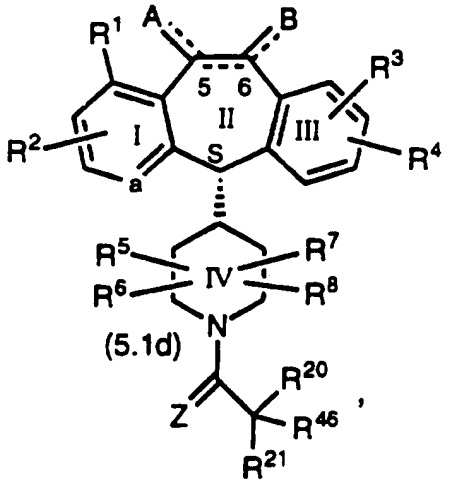
(5.1b),



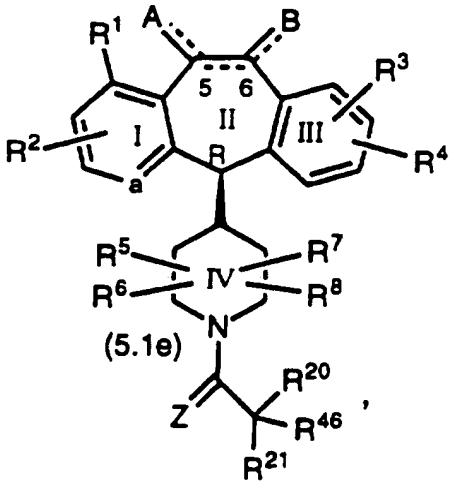
(5.1c),



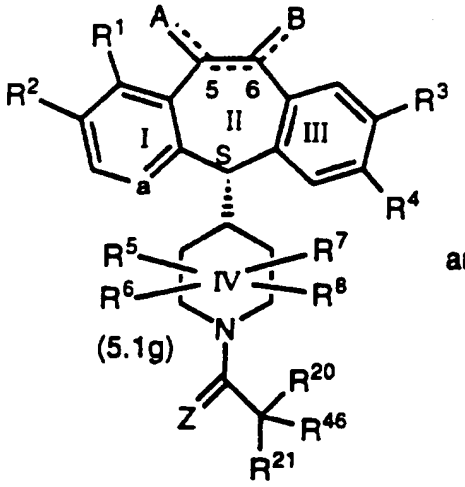
(5.1d),



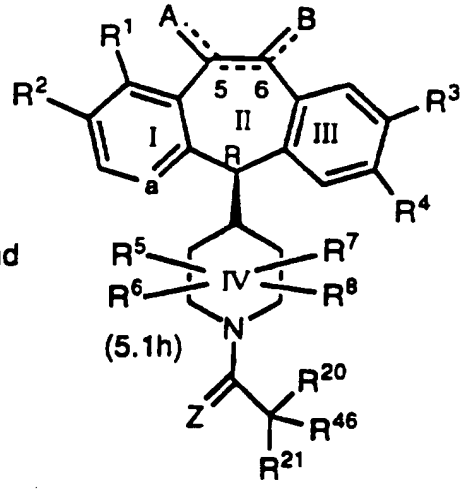
(5.1d),



(5.1e),

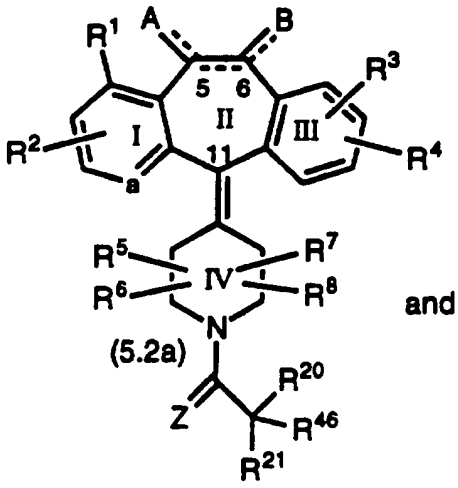


(5.1g) and



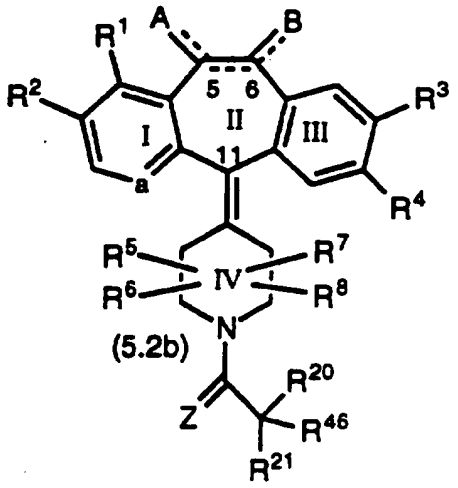
(5.1h)

Compounds of Formula 5.2 additionally include:



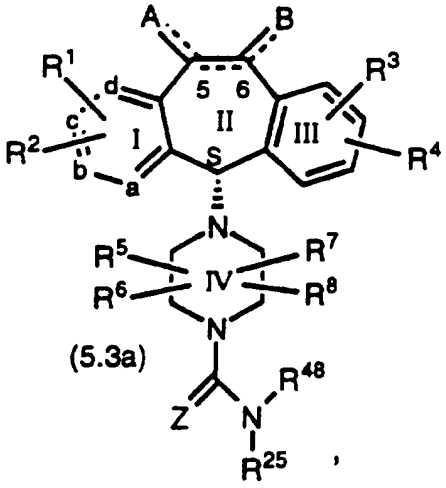
(5.2a)

and

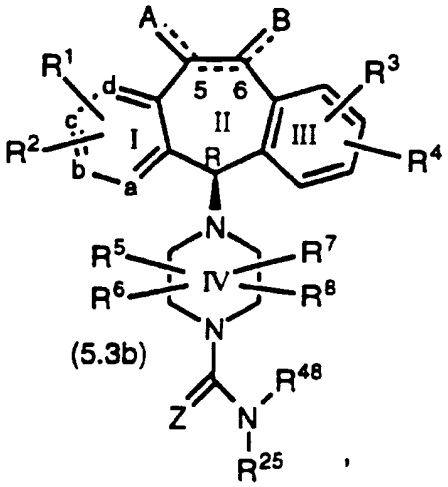


(5.2b)

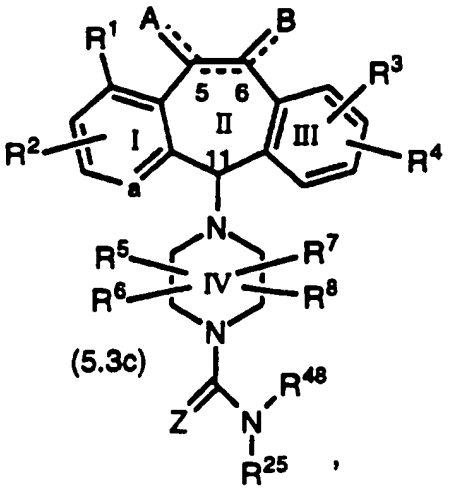
Compounds of Formula 5.3 include:



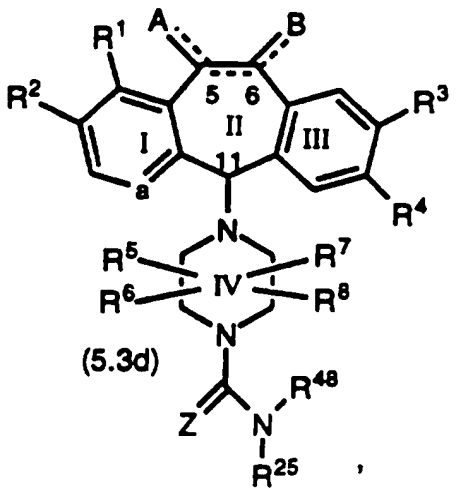
(5.3a),



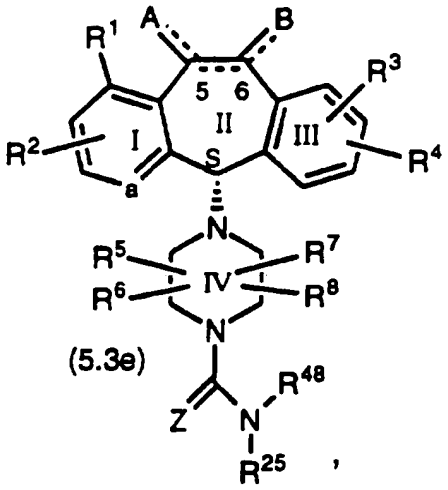
(5.3b),



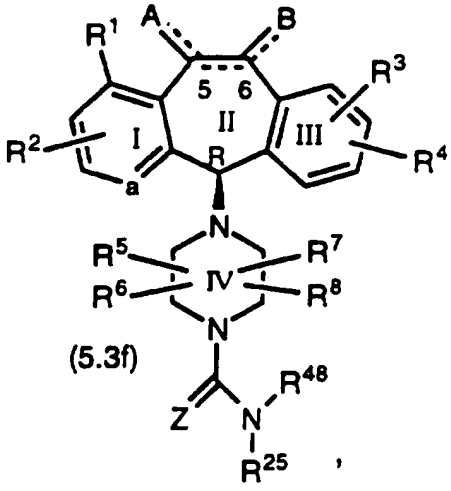
(5.3c) ,



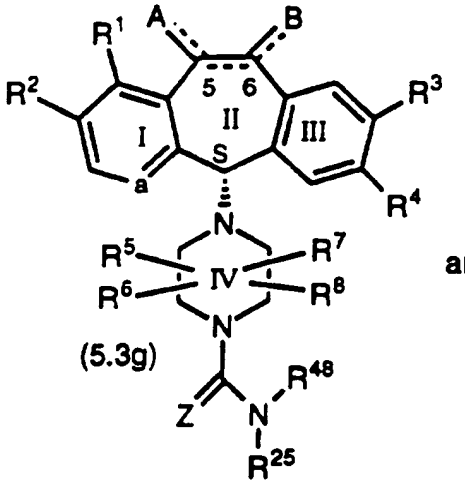
(5.3d) ,



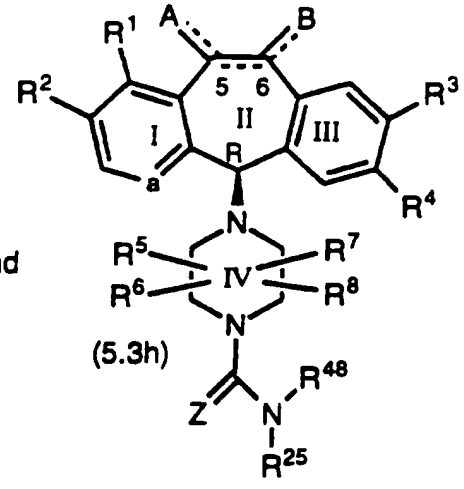
(5.3e) ,



(5.3f) ,

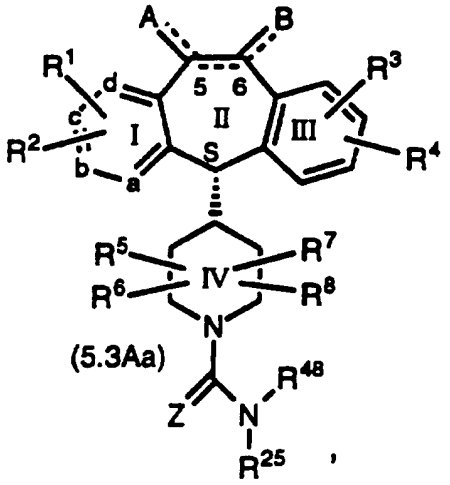


(5.3g) and

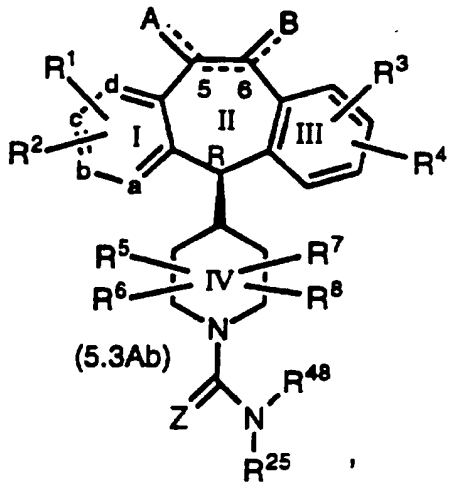


(5.3h)

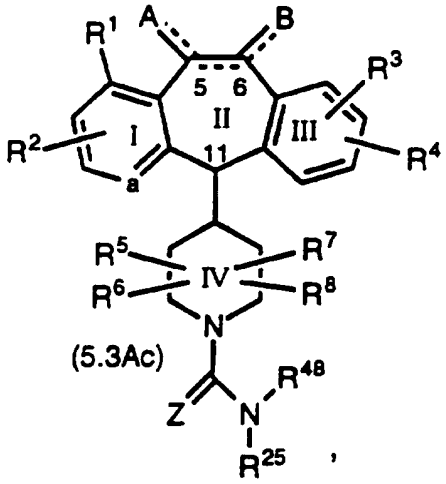
Compounds of formula 5.3A include:



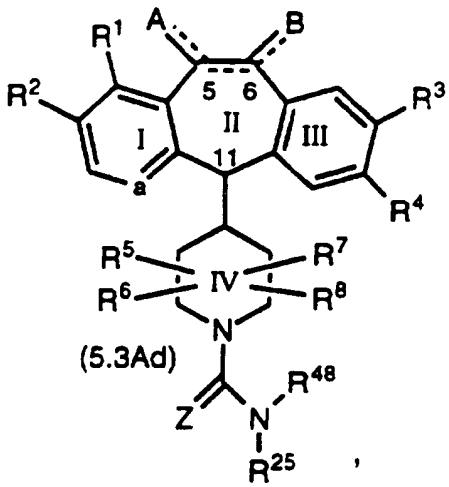
(5.3Aa) ,



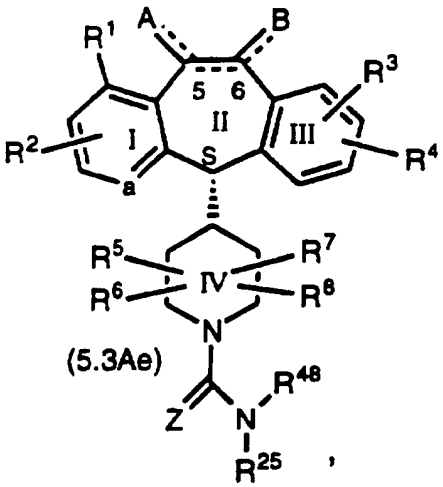
(5.3Ab) ,



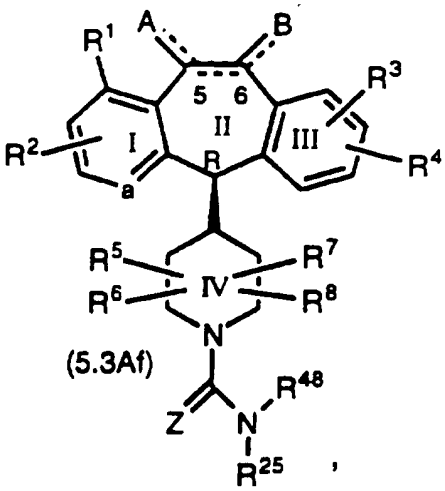
(5.3Ac) ,



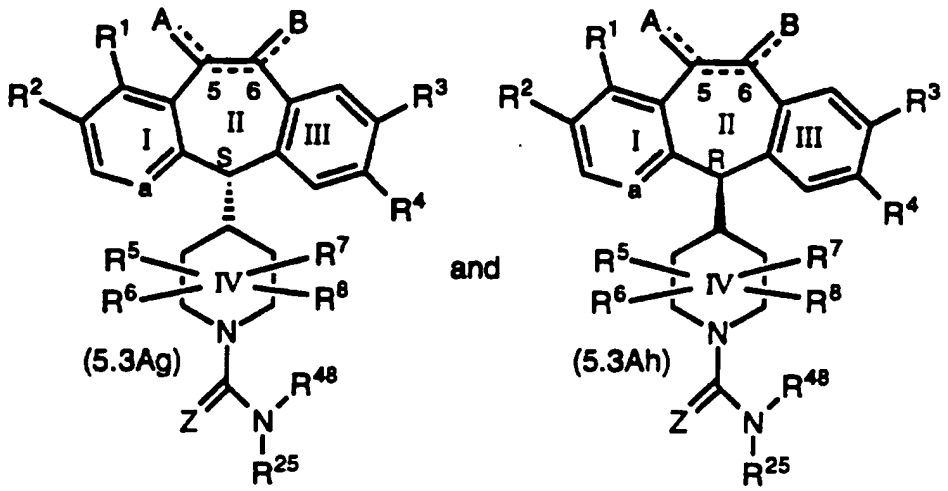
(5.3Ad) ,



(5.3Ae) ,



(5.3Af) ,

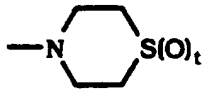


For the compounds of Formulas 5.0, 5.0a-5.0h, 5.1, 5.1a-5.1h, 5.2, and 5.2a-5.2b the definitions of the substituents are as defined for Formula 1.0. For the compounds of Formulas 5.3a-5.3h, 5.3A, and 5.3Aa-5.3Ah, the definitions of the substituents are as defined for Formulas 5.3, 5.3A and 5.3B.

Preferably, for compounds of Formulas 5.0, 5.0a-5.0h, 5.1, 5.1a-5.1h, 5.2, and 5.2a-5.2b, R^{46} is selected from piperidine Ring V, heteroaryl, phenyl, substituted phenyl, substitued pyridyl or substituted pyridyl N-oxide, and R^{20} and R^{21} are independently selected from H or alkyl. Most preferably, R^{46} is pyridyl, pyridyl N-oxide or piperidine Ring V. More preferably, R^{46} is pyridyl, pyridyl N-oxide or piperidine Ring V and both R^{20} and R^{21} are hydrogen or both R^{20} and R^{21} are alkyl (still more preferably methyl).

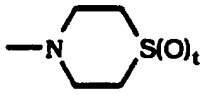
Even more preferably, R^{46} is selected from 3-pyridyl, 4-pyridyl, 3-pyridyl N-oxide, 4-pyridyl N-oxide, 4-N-methylpiperidinyl, 3-N-methylpiperidinyl, 4-N-acetylpiperidinyl or 3-N-acetylpiperidinyl, and both R^{20} and R^{21} are hydrogen or both R^{20} and R^{21} are alkyl (still even more preferably methyl). Even still more preferably, R^{46} is selected from 3-pyridyl, 3-pyridyl N-oxide, 4-pyridyl, and 4-pyridyl N-oxide, and both R^{20} and R^{21} are hydrogen or both R^{20} and R^{21} are methyl.

For compounds of Formulas 5.0, 5.0a-5.0h, 5.1, 5.1a-5.1h, 5.2, and 5.2a-5.2b, when R^1, R^2, R^3, R^4, A and B are selected as described in the proviso at the end of the definition of Formula 1.0, then R^{46} is preferably selected from: triazolyl, 1-N-methylpiperazinyl, 1-piperazinyl or a heterocycloalkyl group of the formula



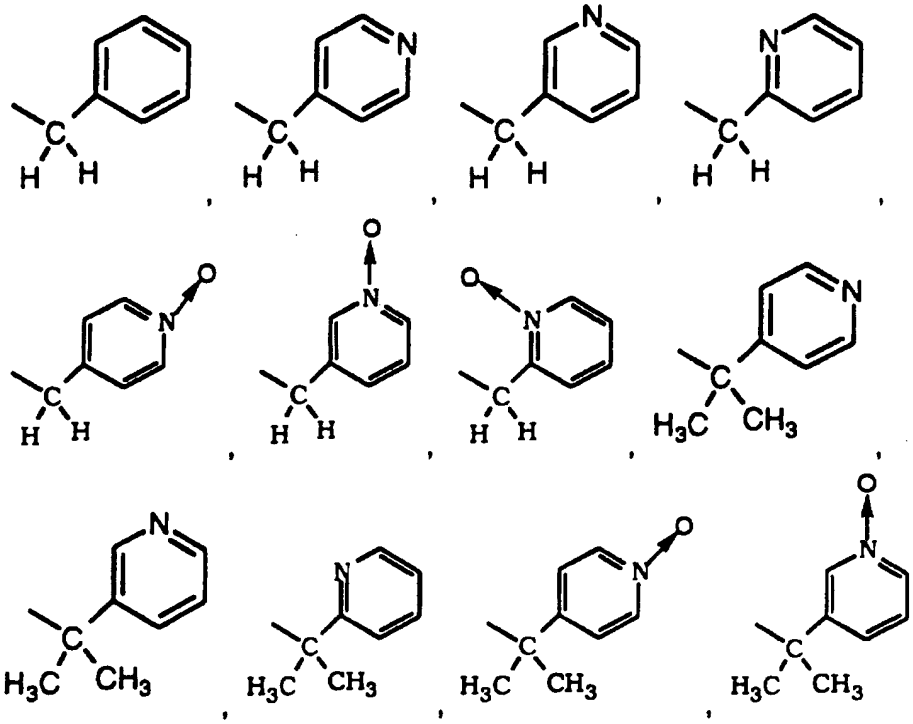
;

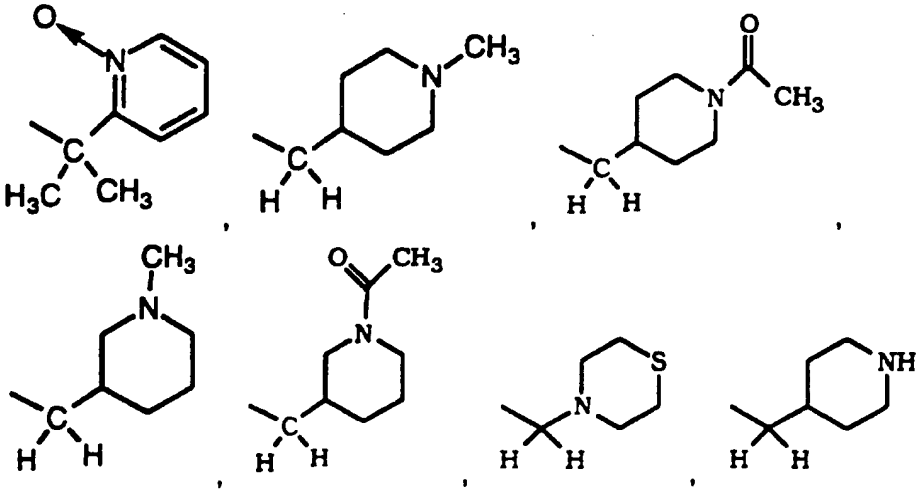
with 1-N-methylpiperazinyl, 1-piperazinyl, or a heterocycloalkyl group of the formula

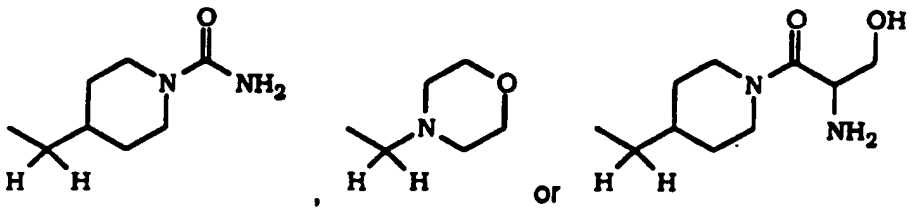


being more preferred.

Examples of the R^{42} groups include:

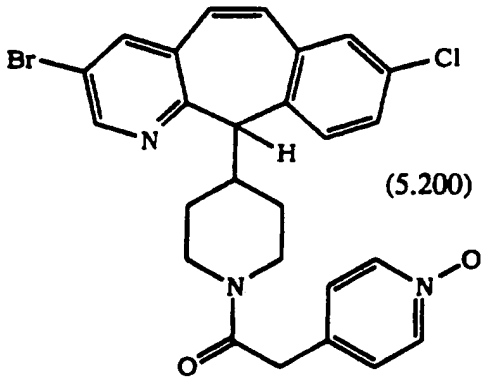




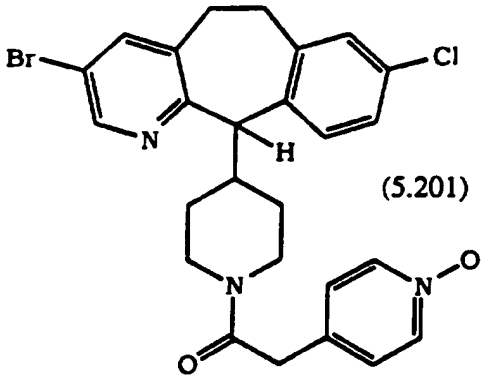


Preferably for the compounds of Formulas 5.3, 5.3a-5.3h, 5.3A, 5.3Aa-5.3Ah, and 5.3B, R^{25} represents phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, or 2-, 3- or 4-pyridyl N-oxide, and most preferably 4-pyridyl or 4-pyridyl N-oxide. More prefereably, R^{48} represents H or methyl and still more preferably H.

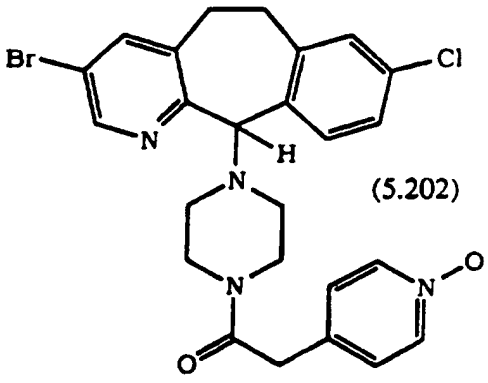
Representative compounds of the invention include:



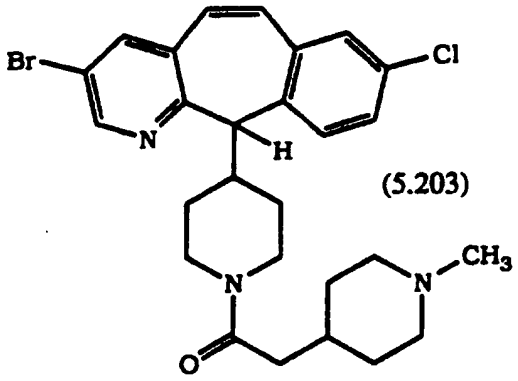
(5.200)



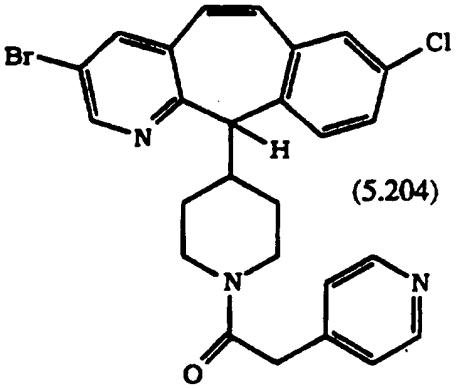
(5.201)



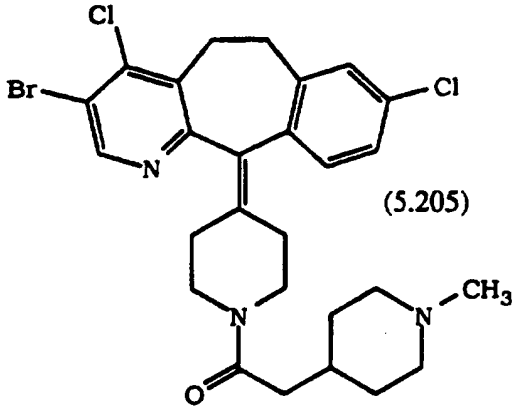
(5.202)



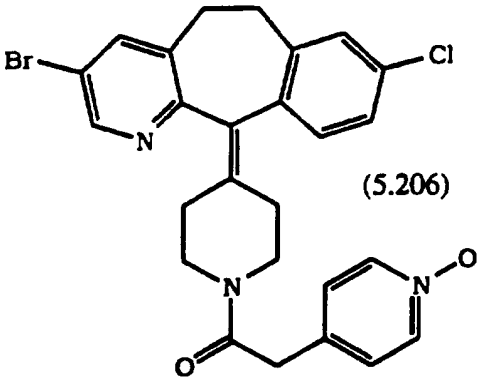
(5.203)



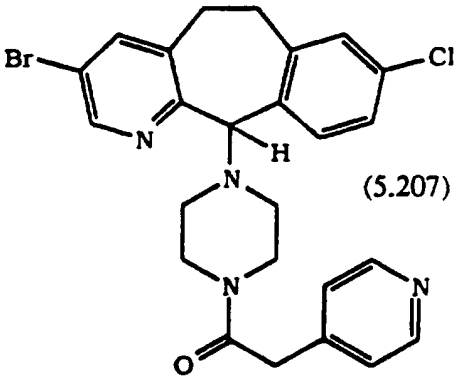
(5.204)



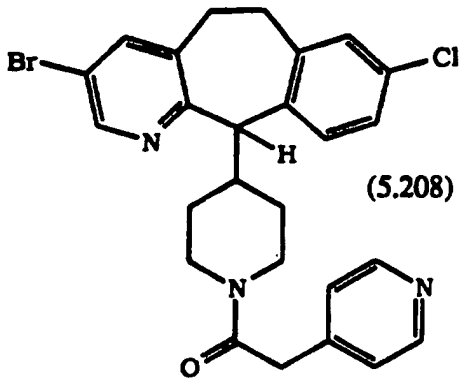
(5.205)



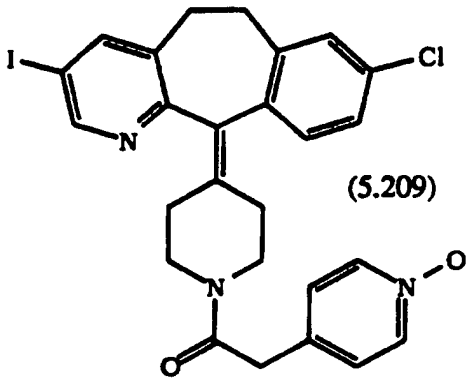
(5.206)



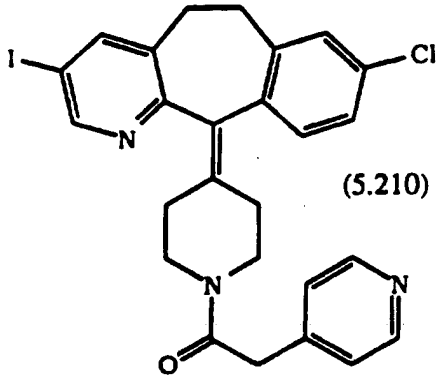
(5.207)



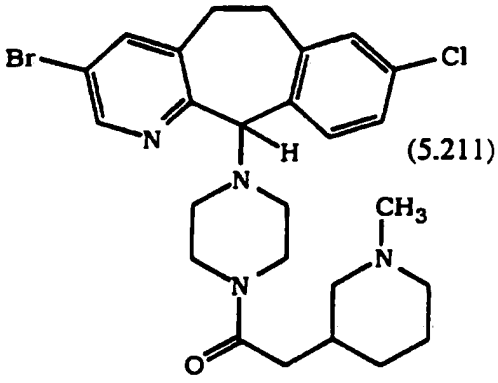
(5.208)



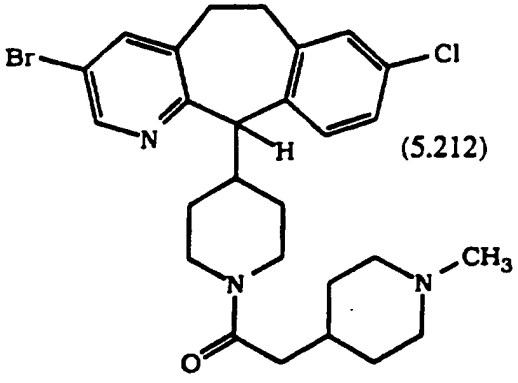
(5.209)



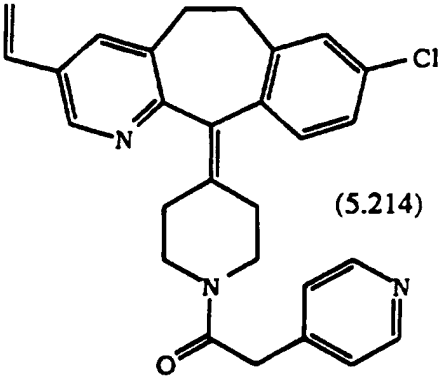
(5.210)



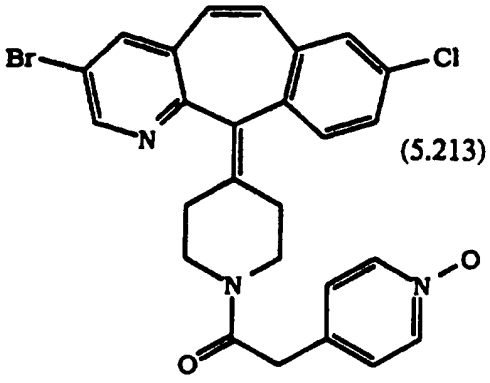
(5.211)



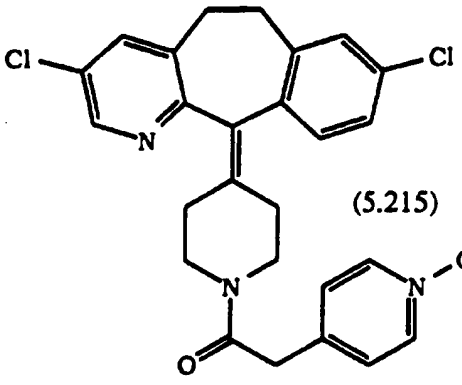
(5.212)



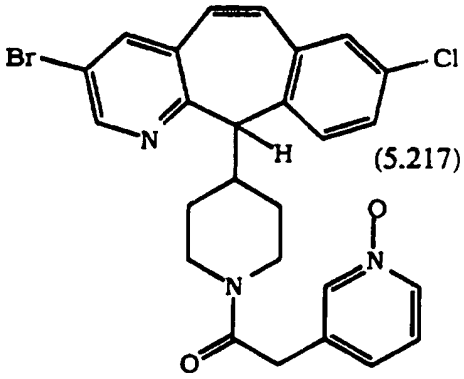
(5.214)



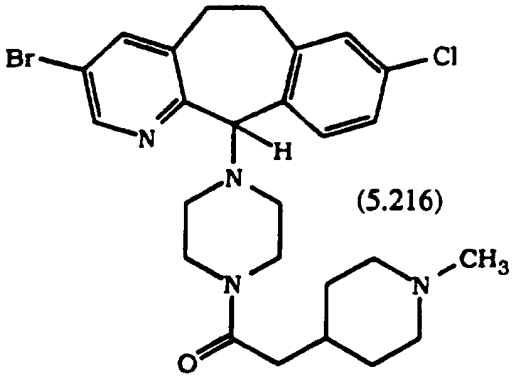
(5.213)



(5.215)

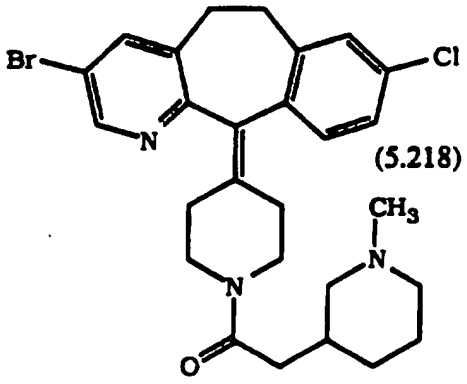


(5.217)

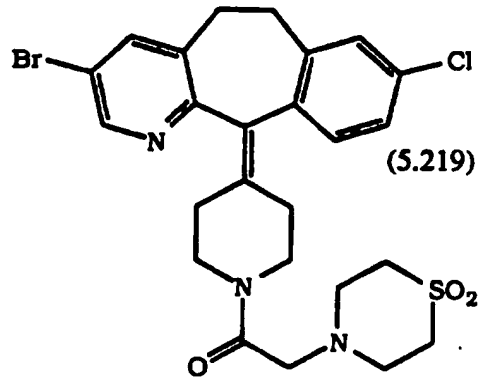


(5.216)

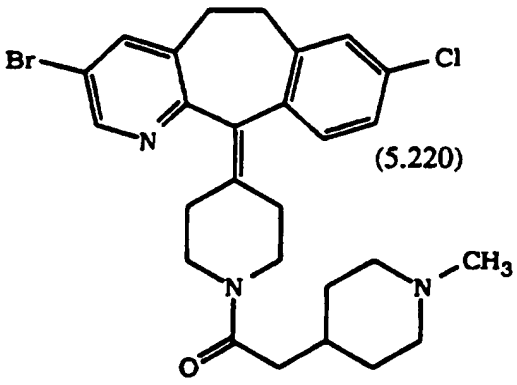
5



(5.218)



(5.219)



(5.220)

Preferred compounds are the compounds of Examples: 426, 400-G, 400-C, 400-F, 400-E, 425-H, 401, 400-B, 400, 400-L, 425-U, 413, 400-J, 417-B, 438, 411-W, 425-O, 400-D, 400-K, 410-G and 400-H.

Lines drawn into the ring systems indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

Certain compounds of the invention may exist in different isomeric (e.g., enantiomers and diastereoisomers) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

Certain tricyclic compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Certain basic tricyclic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-

nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purpopses of the invention.

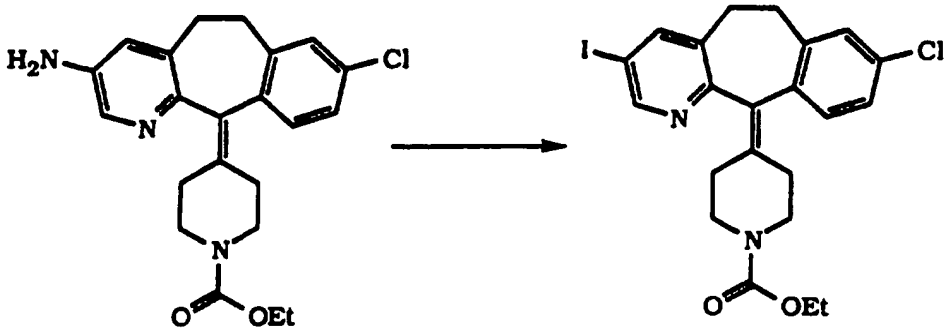
Compounds of the invention may be made by the methods described in the examples below, and by the methods described in WO 95/10516 published April 20, 1995--see, for example, the methods for preparing compounds of Formula 400.00.

On page 57 at lines 7 to 16 of WO 95/10516 a process is disclosed for introducing substituents at the C-3 position of pyridine Ring I of Formula 1.0 by nitrating a compound of Formula 415.00. The nitro group may then be reduced to the corresponding amine using the disclosed reagents or powdered Zn and either $CuCl_2$ or $CuBr_2$ in aqueous EtOH .

Compounds useful in this invention are exemplified by the following preparative examples, which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

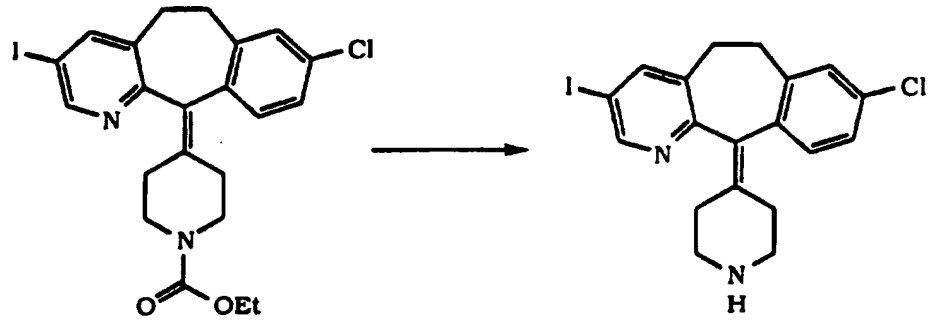
PREPARATIVE EXAMPLE 48

Step A:



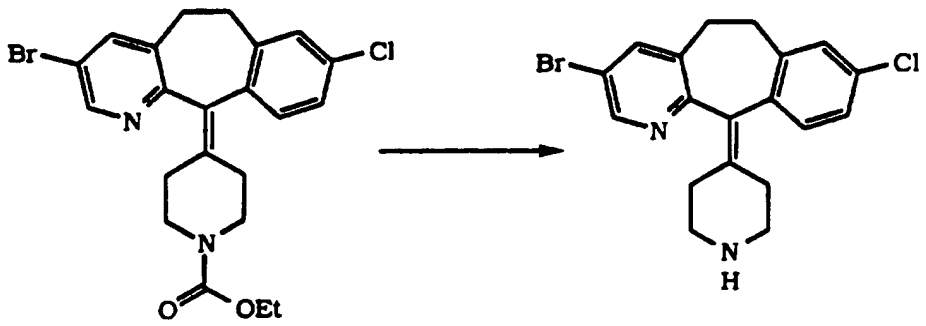
Combine 6 g (15.11 mmol) of the title compound of Preparative Example 47B, of WO 95/10516, and benzene, and add 2.3 g (9.06 mmol) of iodine. Heat the mixture at reflux for 3 hours, cool, then dilute with 50 mL of CH_2Cl_2. Wash the organic phase with 5% $NaHSO_3$(aqeuous) (3 x 80 mL), then with 1M NaOH (aqueous) (2x 80 mL), and dry over $MgSO_4$. Concentrate to a residue chromatograph (silica gel, 30% EtOAc/hexanes), to give 3.2 g (42% yield) of the product iodo compound. Mass Spec.: MH+ = 509

Step B:



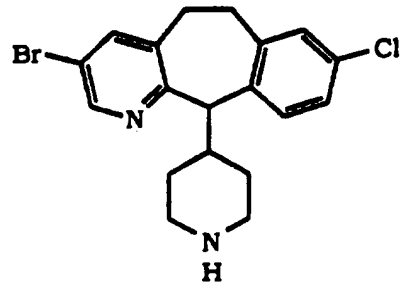
The product of Step A is hydrolyzed via substantially the same procedure as described in Example 358, Step A, of WO 95/10516, to give the iodoamine product in 89% yield.

PREPARATIVE EXAMPLE 49

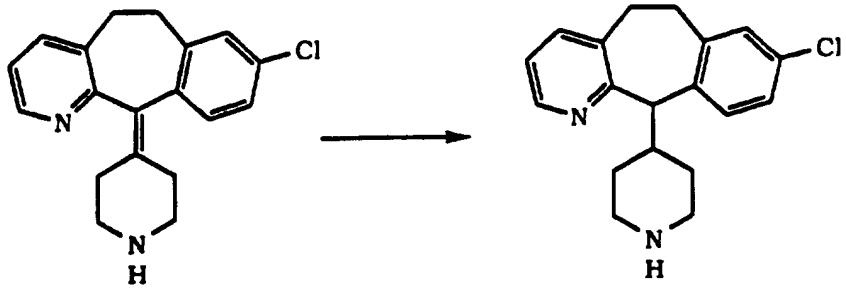


The product of Preparative Example 47, Step C, of WO 95/10516, (2.42 g) is hydrolyzed via substantially the same procedure as described in Example 358, Step A, of WO 95/10516, to give 1.39 g (69% yield) of the bromoamine product.

PREPARATIVE EXAMPLE 51A

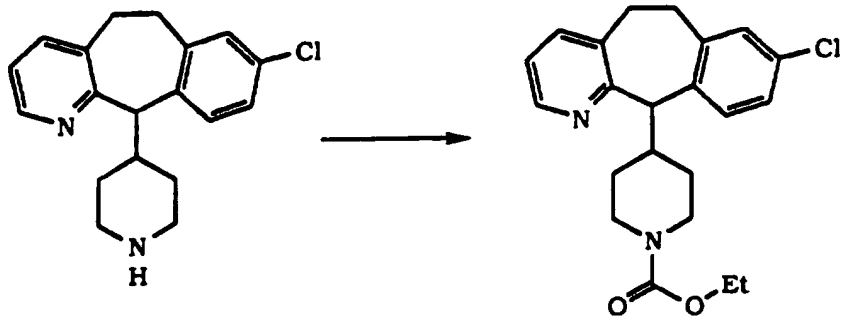


Step A:



Combine 82.0 g (0.26 mole) of the product of Preparative Example 1, Step G, of WO 95/10516, and 1 L of toluene, then add 20.06 g (0.53 mole) of $LiAlH_4$ and heat the reaction mixture at reflux overnight. Cool the mixture to room temperature and add ~1 L of Et_2O, followed by dropwise addition of saturated Na_2SO_4 (aqueous) until a precipitate forms. Filter and stir the filtrate over $MgSO_4$ for 30 minutes, then concentrate *in vacuo* to give the product compound in 83% yield. Mass Spec.: MH^+ = 313

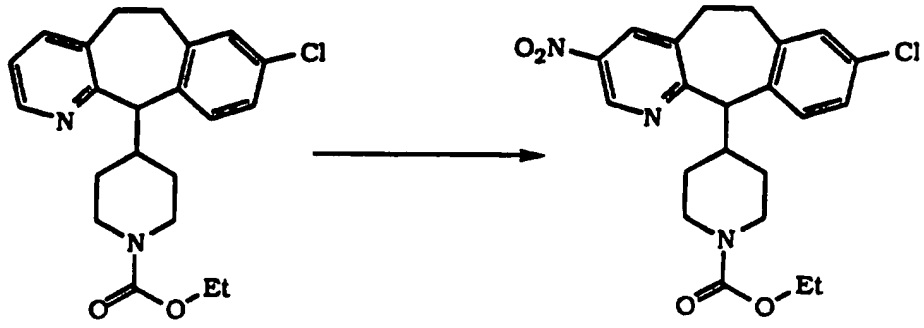
Step B:



Combine 24.32 g (74.9 mmol) of the Product from Step A, 500 mL of toluene, 83 mL of Et_3N and 65.9 mL of ethyl chloroformate and heat the mixture at reflux overnight. Cool to 25°C, pour into 200 mL of water and

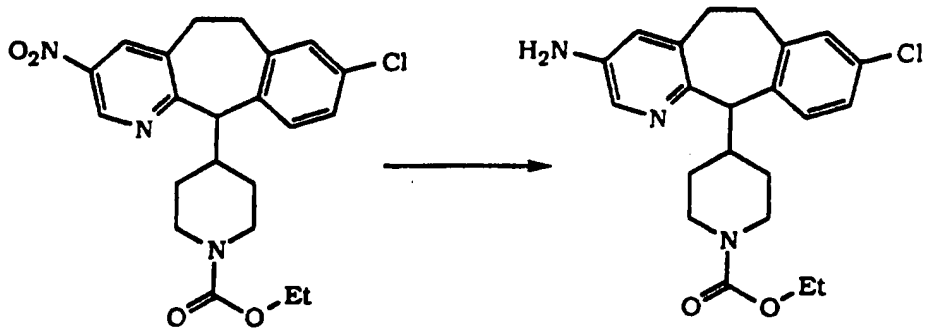
extract with EtOAc. Dry the extract over $MgSO_4$, concentrate *in vacuo* to a residue and chromatograph (silica gel, 50% EtOAc/hexane) to give 15 g of the product compound. Mass Spec.: MH^+ = 385.

Step C:



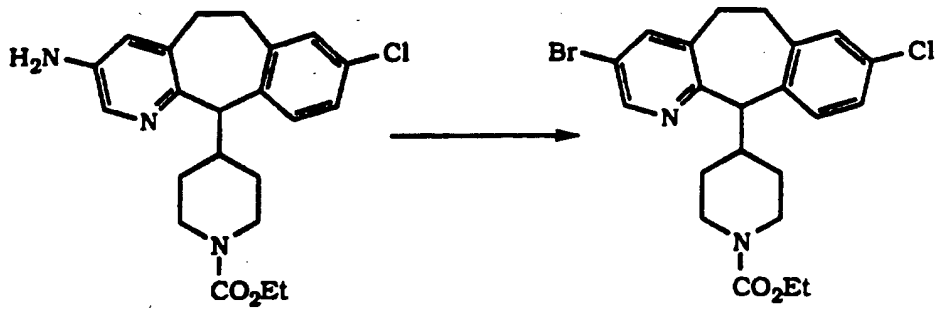
Dissolve 3.2 g (10.51 mmol) of tetra-n-butylammonium nitrate in 25 mL of CH_2Cl_2 and add 2.2 g (10.51 mmol, 1.5 mL) of TFAA. Cool to 0°C and add the mixture (via cannula) to a solution of 3.68 g (9.56 mmol) of the product of Step B in 50 mL of CH_2Cl_2 at 0°C, then stir at 0°C for 3 hours. Allow the mixture to warm to 25°C while stirring overnight, then extract with saturated $NaHCO_3$ (aqueous) and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 30% EtOAc/hexane) to give 1.2 g of the product compound. Mass Spec.: MH^+ = 430

Step D:



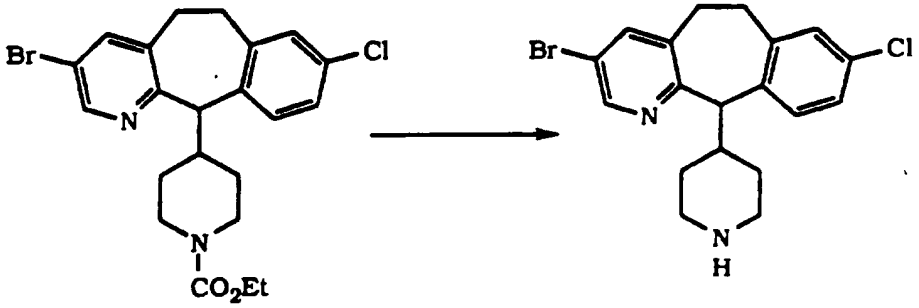
Combine 2.0 g (4.7 mmol) of the Product of Step C and 150 mL of 85% EtOH (aqueous), add 2.4 g (42 mmol) of Fe filings and 0.24 g (2.1 mmol) of $CaCl_2$, and heat at reflux for 16 hours. Filter the hot mixture through a bed of celite®, wash the celite® with hot EtOH. Concentrate the filtrate *in vacuo* to give a 100% yield of the product compound. Mass Spec.: MH^+ = 400.

Step E:



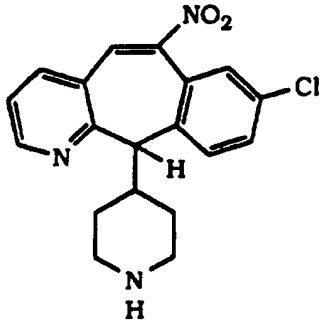
Combine 2.0 g (5.2 mmol) of the Product of Step D and 20 mL of 48% HBr, cool the mixture to -5°C. Stir the mixture at -5°C for 15 minutes and slowly add a solution of 1.07 g (15.5 mmol) of $NaNO_2$ in 10 mL of water. Stir for 45 minutes, then quench with 50% NaOH (aqueous) to pH ~10. Extract with EtOAc, dry the combined extracts over $MgSO_4$ and concentrate *in vacuo* to give the product compound. Mass Spec.: MH^+= 465

Step F:

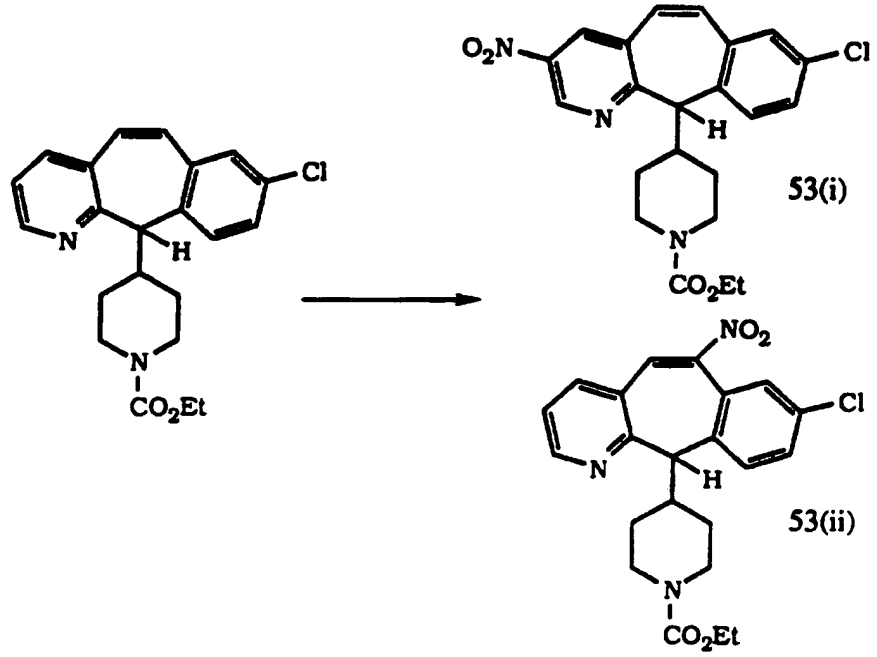


Hydroyze 4.0 g of the Product of Step E via substantially the same process as described for Example 358, Step A, of WO 95/10516, to give 1.39 g of the product compound. Mass Spec.: MH^+ = 392

PREPARATIVE EXAMPLE 53



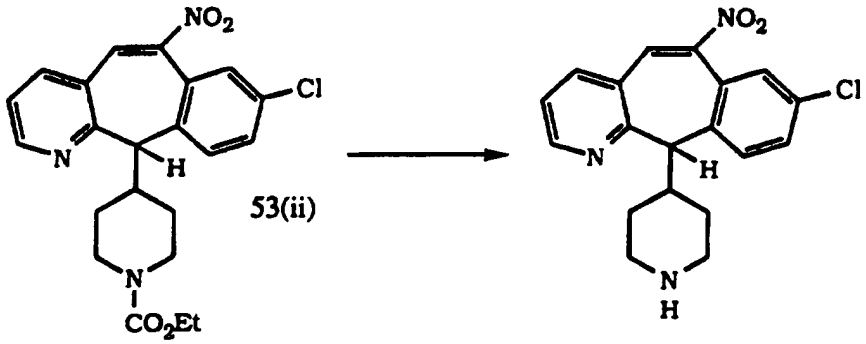
Step A:



Combine 14.95 g (39 mmol) of the Product of Preparative Example 34A, of WO 95/10516, and 150 mL of CH_2Cl_2, then add 13.07 g (42.9 mmol) of $(nBu)_4NNO_3$ and cool the mixture to 0°C. Slowly add (dropwise) a solution of 6.09 mL (42.9 mmol) of TFAA in 20 mL of CH_2Cl_2 over 1.5 hours. Keep the mixture at 0°C overnight, then wash successively with saturated $NaHCO_3$ (aqueous), water and brine. Dry the organic solution over Na_2SO_4, concentrate *in vacuo* to a residue and chromatograph the residue (silica gel, EtOAc/hexane gradient) to give 4.32 g and 1.90 g of the two product compounds 53(i) and 53(ii), respectively.

Mass Spec.(53(i)): MH^+ = 428.2; Mass Spec. (53(ii)): MH^+ = 428.3

Step B:

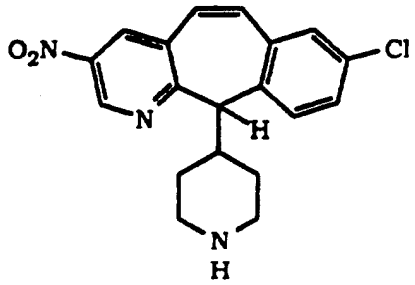
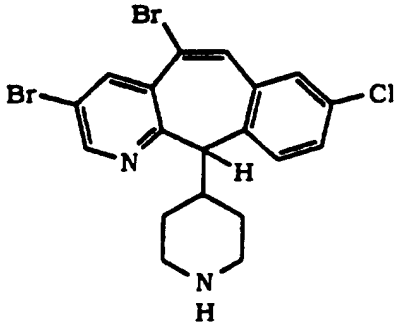
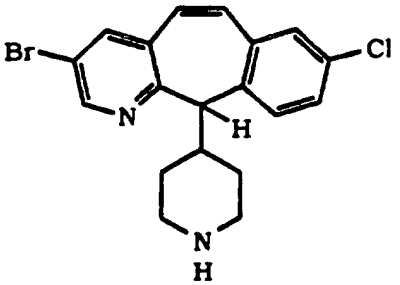


The compound 53(ii) from Step A (0.20 g) is hydrolyzed via substantially the same procedure as described for Example 358, Step A,

of WO 95/10516 (published April 20, 1995), to give 0.16 g of the product compound.

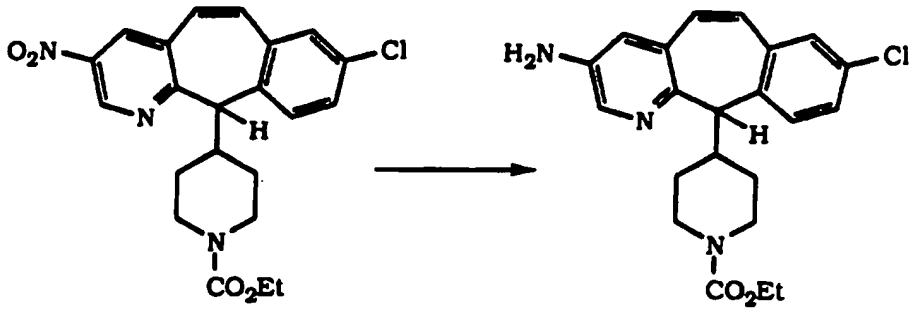
Using the starting compound indicated and substantially the same procedure as described in Preparative Example 53, Step B, the compounds in Table 1 are prepared:

TABLE 1

Starting Compound	Compound	Analytical Data
Preparative Example 53, Step A, compound 53(i)	 Preparative Example 53A	---
Preparative Example 54, Step B, compound 54(ii)	 Preparative Example 53B	Mass Spec.: MH^+ = 466.9
Preparative Example 54, Step B, compound 54(i)	 Preparative Example 53C	Mass Spec.: MH^+ = 466.9

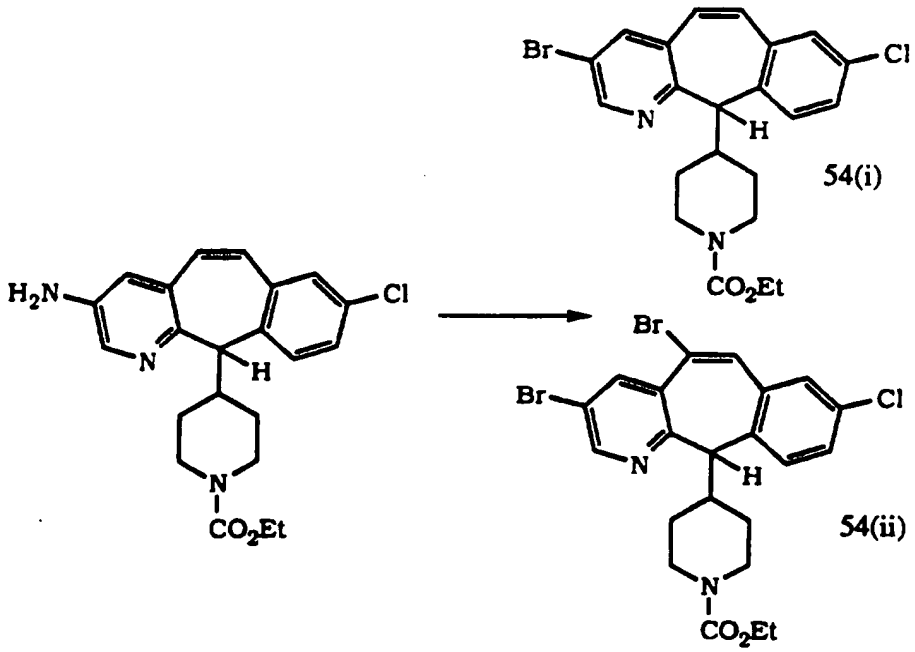
PREPARATIVE EXAMPLE 54

Step A:



Combine 22.0 g (51.4 mmol) of the product 53(i) from Preparation 53, Step A, 150 mL of 85% EtOH (aqueous), 25.85 g (0.463 mole) of Fe powder and 2.42 g (21.8 mmol) of $CaCl_2$, and heat at reflux overnight. Add 12.4 g (0.222 mole) of Fe powder and 1.2 g (10.8 mmol) of $CaCl_2$ and heat at reflux for 2 hours. Add another 12.4 g (0.222 mole) of Fe powder and 1.2 g (10.8 mmol) of $CaCl_2$ and heat at reflux for 2 hours more. Filter the hot mixture through celite®, wash the celite® with 50 mL of hot EtOH and concentrate the filtrate *in vacuo* to a residue. Add 100 mL of anhydrous EtOH, concentrate to a residue and chromatograph the residue (silica gel, MeOH/CH_2Cl_2 gradient) to give 16.47 g of the product compound.

Step B:

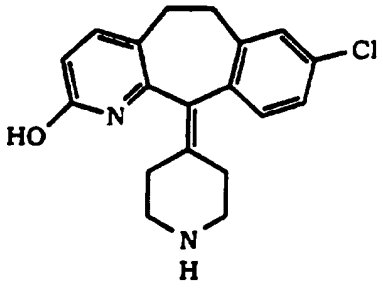


Combine16.47 g (41.4 mmol) of the product compound from Preparative Example 54, Step A, and 150 mL of 48% HBr (aqueous) and

cool to -3°C. Slowly add (dropwise) 18 mL of bromine, then slowly add (dropwise) a solution of 8.55 g (0.124 mole) of $NaNO_2$ in 85 mL of water. Stir for 45 minutes at -3° to 0°C, then adjust to pH = 10 by adding 50% NaOH (aqueous). Extract with EtOAc, wash the extracts with brine and dry the extracts over Na_2SO_4. Concentrate to a residue and chromatograph (silica gel, EtOAc/hexane gradient) to give 10.6 g and 3.28 g of the two product compounds 54(i) and 54(ii), respectively.

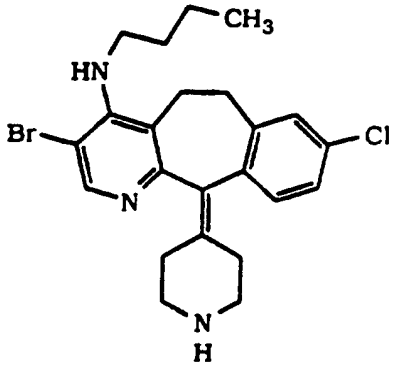
Mass Spec. (54(i)): MH^+ = 461.2; Mass Spec. (54(ii)): MH^+ = 539

PREPARATIVE EXAMPLE 55

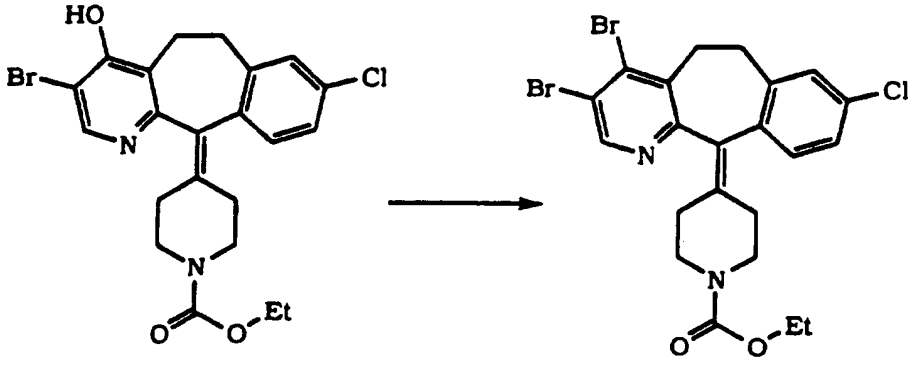


The title compound is known and is prepared by the procedure described in Bioorg. & Med. Chem. Lett., 3, (No. 6) 1073-1078 (1993).

PREPARATIVE EXAMPLE 56

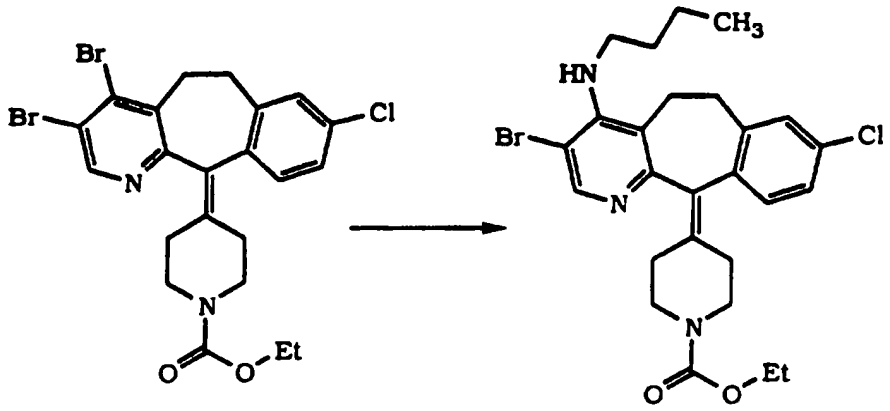


Step A:



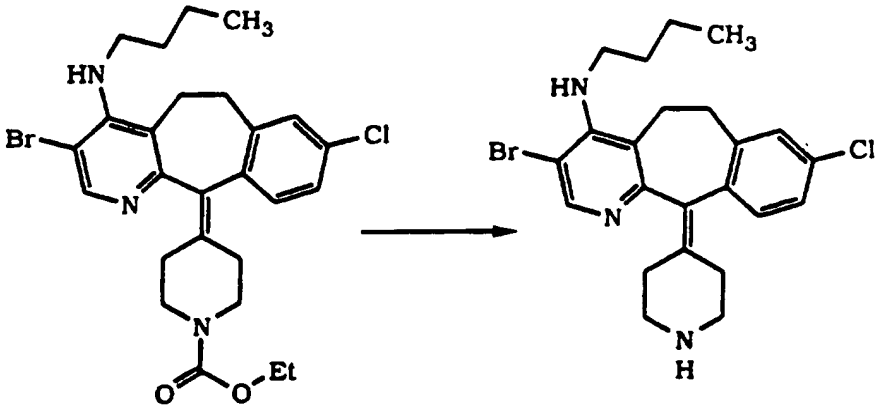
Combine 2.04 g of the product of Preparative Example 44, of WO 95/10516 (published April 20, 1995), 1.3 mL of PBr_3, 1.0 mL of Et_3N and 20 mL of CH_2Br_2, and heat the mixture at reflux overnight. Cool the mixture, dilute with CH_2Cl_2 and wash with 1 N NaOH (aqueous). Dry over $MgSO_4$ and concentrate *in vacuo* to give 1.22 g (53% yield) of the product compound. Mass Spec.: $MH^+ = 541$

Step B:



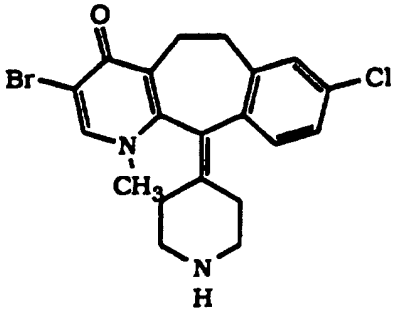
Combine 0.3 g of the product compound from Preparative Example 56, Step A, and 8 mL of n-butylamine and stir at 120°C in a sealed tube for 48 hours. Concentrate *in vacuo* to a residue and purify by preparative plate chromatography (silica gel, 1.5-2.5% $MeOH/CH_2Cl_2$) to give 80 mg (27%) yield of the product compound. Mass Spec.: $MH^+ = 534$

Step C:

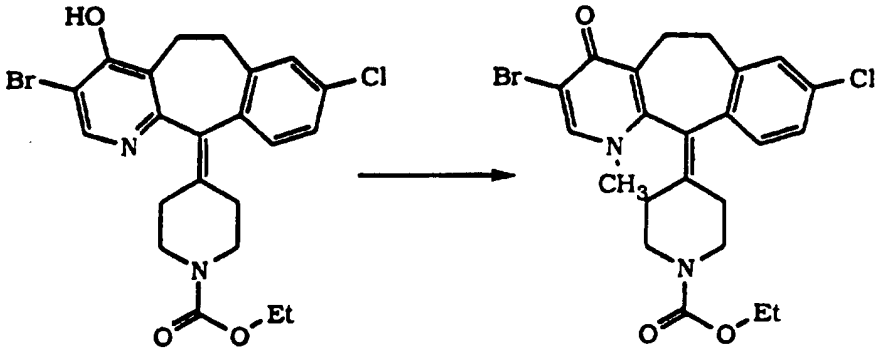


Combine 66 mg of the product compound from Preparative Example 56, Step B, 4 mL of anhydrous EtOH, and 15 mL of concentrated HCl stir at reflux for 60 hours. Cool the reaction mixture to about 0°C and basify by adding KOH. Extract with CH_2Cl_2, dry the extract over $MgSO_4$, and concentrate *in vacuo* to give 46 mg (81% yield) of the product compound. Mass Spec.: $MH^+ = 462$

PREPARATIVE EXAMPLE 57

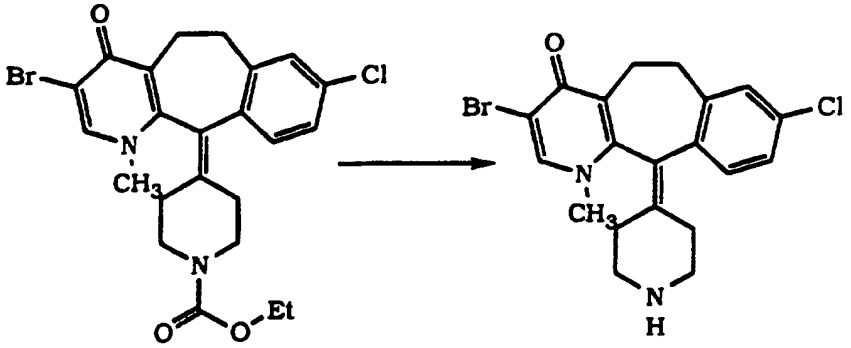


Step A:



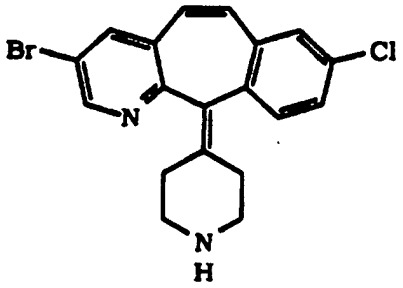
Combine 1.19 g of the product of Preparative Example 44, of WO 95/10516, 10 mL of anhydrous DMF, 0.2 g of NaH (60% in mineral oil) and 0.19 mL of methyl iodide, and stir at room temperature overnight. Concentrate *in vacuo* to a residue, dilute the residue with CH_2Cl_2, wash with saturated $NaHCO_3$ (aqueous), and dry over $MgSO_4$. Concentrate *in vacuo* to give 1.13 g (92% yield) of the product compound. Mass Spec.: MH^+ = 493.

Step B:

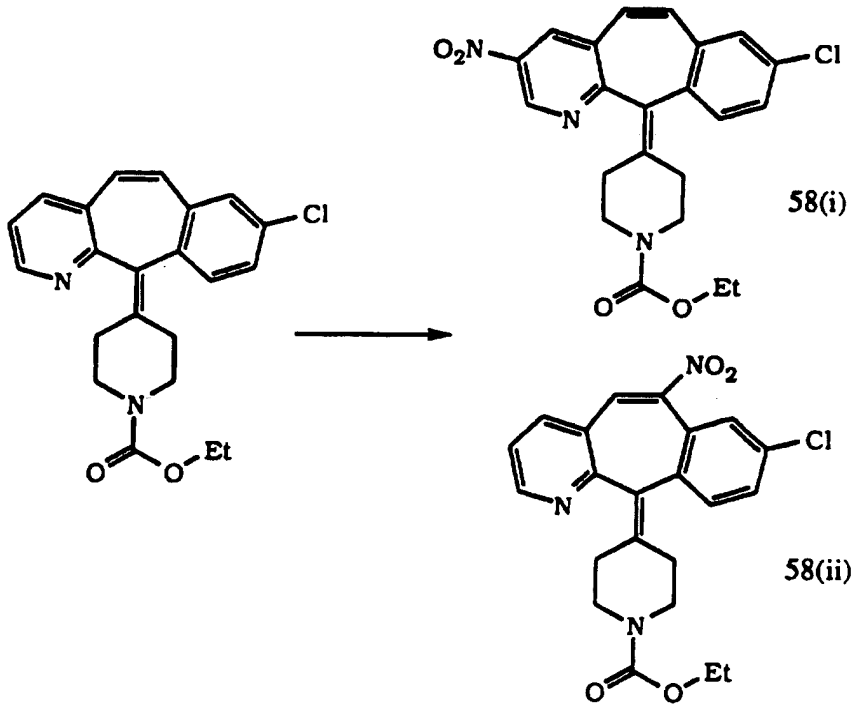


Hydrolyze 1.13 g of the product of Step A via substantially the same procedure as described for Preparative Example 56, Step C, to give 0.61 g (63% yield) of the product compound.

PREPARATIVE EXAMPLE 58



Step A:

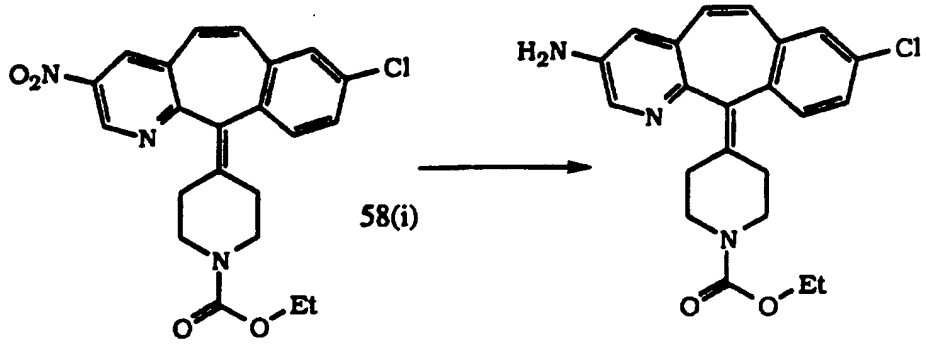


58(i)

58(ii)

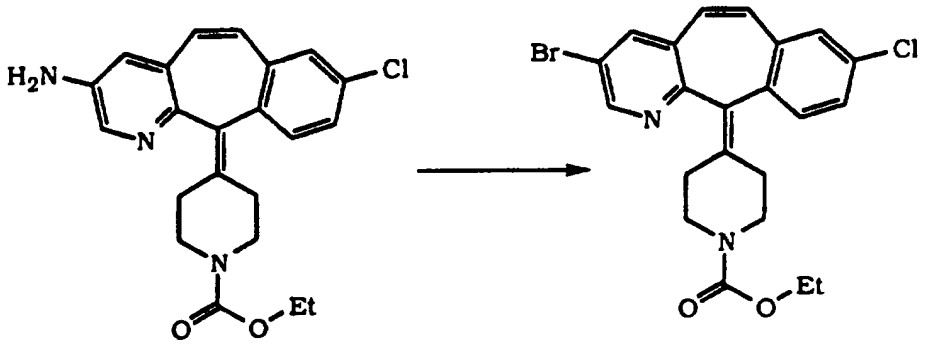
Combine 1.07 g (3.52 mmol) of tetrabutylammonium nitrate, 4 mL of anhydrous CH_2Cl_2 and 0.743 g (3.52 mmol) of TFAA, and add the resulting mixture to a solution of 1.22 g (3.20 mmol) of the title compound of Preparative Example 37, of WO 95/10516, in 8 mL of anhydrous CH_2Cl_2 at room temperature. Stir at room temperature overnight, then wash with 20 mL of saturated $NaHCO_3$ (aqueous) and 20 mL of brine, and dry over $MgSO_4$. Concentrate *in vacuo* and chromatograph the resulting residue (silica gel, EtOAc/hexane) to give 0.216 g of the product compound 58(i) and 0.27 g of the product compound 58(ii). Mass Spec. (58(i)): MH^+ =426. m.p. (58(i)) 97.5° - 99.2°C.

Step B:



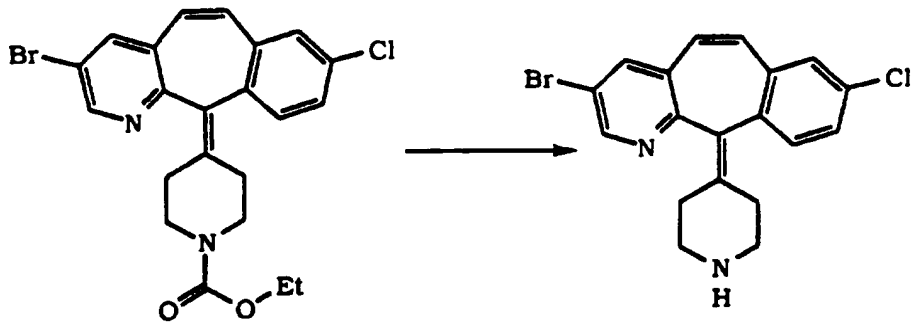
Reduce the product 58(i) from Step A via essentially the same procedure as described in Preparative Example 47, Step B, of WO 95/10516, to give the product compound. Mass Spec.: MH^+ = 396

Step C:



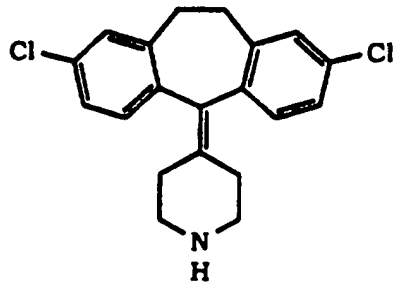
React the product from Step B with HBr and bromine via essentially the same procedure as described in Preparative Example 47, Step C, of WO 95/10516, to give the product compound. Mass Spec.: MH^+ = 459

Step D:

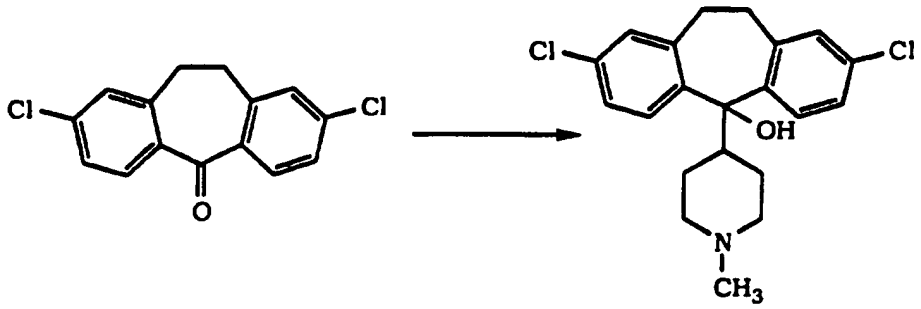


Hydrolyze 0.83 g of the product from Step C via essentially the same procedure as described in Preparative Example 56, Step C, to give 0.56 g of the product compound. Mass Spec.: MH^+ = 387

PREPARATIVE EXAMPLE 59

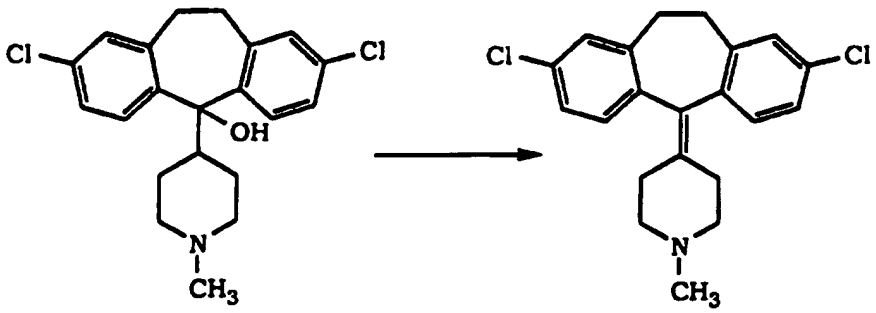


Step A:



Combine 7.3 g (26.4 mmol) of the starting ketone (see J. Med. Chem., 4238 (1992)) and 230 mL of THF and cool to 0°C. Add a solution of 32.2 mmol) of N-methyl-piperidine-4-magnesium bromide in 26 mL of THF and stir at 0°-5°C for 4 hours. Add 400 mL of EtOAc, wash with saturated NH_4Cl (aqueous), and dry over $MgSO_4$. Concentrate *in vacuo* to a residue, add ~200 mL of CH_2Cl_2 and stir for 0.5 hours. Filter to collect the resulting solid and concentrate the filtrate to a volume of ~100 mL and let sit at 5 °C for 18 hours. Filter and combine the solids to obtain a total of 7 g (19.4 mmol) of the product compound. m.p.=153.7°-158 °C; Mass Spec.: (Cl) MH^+ = 376

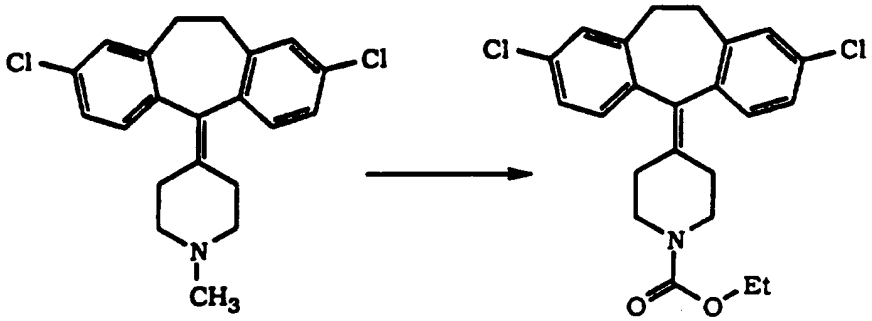
Step B:



Combine 5 g of the product from Step A and 30 mL of TFA at ambient temperature and stir for 1 hour. Concentrate *in vacuo* to a residue, dissolve the residue in CH_2Cl_2 and wash with a saturated

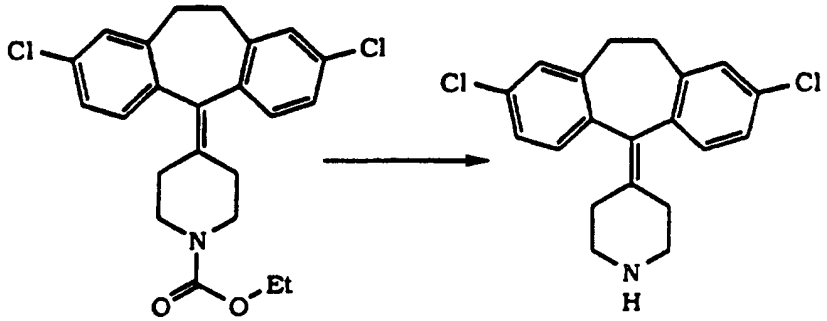
$NaHCO_3$ (aqueous). Concentrate *in vacuo* to give 4.64 g of the product compound. m.p.= 136.7°-138°C; Mass Spec.: (FAB) MH^+ = 358.1

Step C:



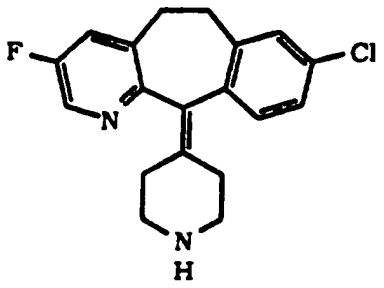
Combine 0.6 g (1.75 mmol) of the product of Step B and 25 mL of toluene, add 0.73 mL (5.27 mmol) of Et_3N and 1.34 mL (14 mmol) of $ClCO_2Et$, and heat to 80°C for 2 hours. Add 0.7 mL more of $ClCO_2Et$, heat for 1 more hour, then cool to 25 °C and concentrate *in vacuo* to a residue. Dissolve the residue in EtOAc and wash with 1N NaOH (aqueous) followed by brine. Dry over $MgSO_4$, concentrate *in vacuo* to a residue and chromatograph (silica gel, 10% EtOAc/hexanes) to give 0.55 g of the product compound. Mass Spec.: (FAB) MH^+ = 416.2

Step D:

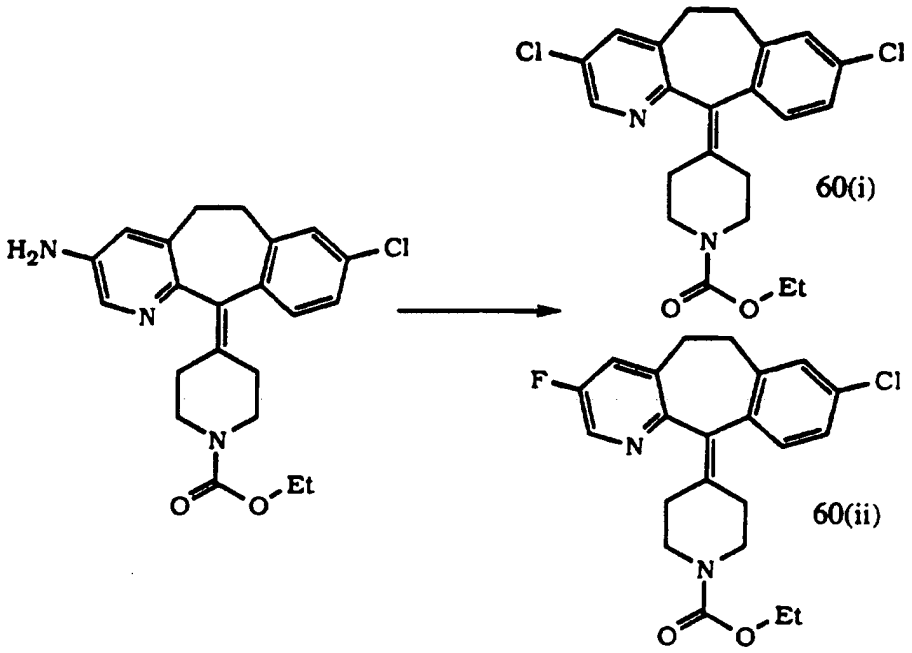


Dissolve 5 g (12.5 mmol) of the product of Step C in 30% HBr in HOAc and heat at 40°C for 24 hours, then cautiously add the mixture to cold 25 % NaOH (aqueous). Extract with CH_2Cl_2 (3 X 100 mL), concentrate the extracts to a residue and chromatograph (silica gel, 5% to 30 % MeOH/CH_2Cl_2) to give 2.18 g of the product compound. m.p.= 159.5°-160.8°C; Mass Spec.: (FAB) MH^+ = 344.1

PREPARATIVE EXAMPLE 60

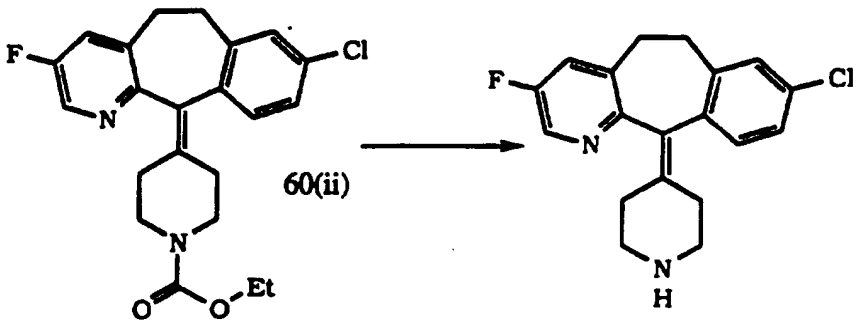


Step A:



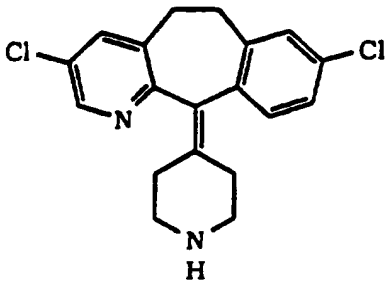
Combine 16.25 g (40.83 mmol) of the product of Preparative Example 47, Step B, of WO 95/10516, and a slurry of 7.14 g (61.11 mmol) of $NOBF_4$ in 100 mL of CH_2Cl_2 and stir the mixture for 3 hours. Add 100 mL of o-dichlorobenzene and heat for 5 hours, distilling the CH_2Cl_2 from the mixture. Concentrate *in vacuo* to a residue, add 200 mL of CH_2Cl_2 and wash with water (2 X 200 mL). Dry over $MgSO_4$, concentrate *in vacuo* to a residue, and chromatograph (silica gel, 20% EtOAc/hexane) to give 4.1 g of product compound 60(i) and 4.01 g of Product compound 60(ii). Mass Spec. (60 (i)): MH^+ = 418. Mass Spec. (60 (ii)): MH^+ = 401

Step B:



Hydrolyze 3.4 g of the product 60 (ii) from Step A via essentially the same process as described for Example 358, Step A, of WO 95/10516, to give 3.01 g of product compound. Mass Spec.: MH^+ = 329

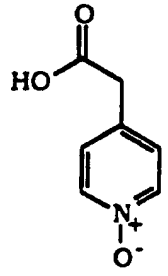
Using compound 60(i) from Preparative Example 60, Step A, and following substantially the same procedure as described in Preparative Example 60, Step B, the compound:



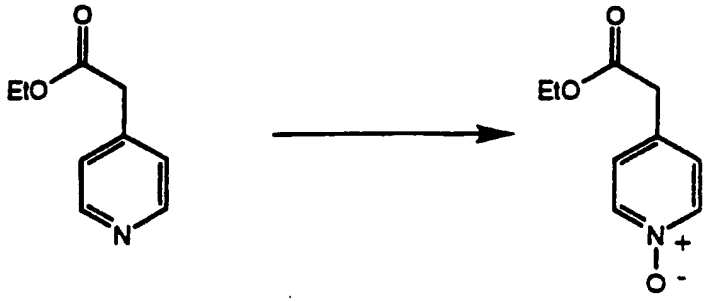
(Preparative Example 60A)

was prepared. Mass Spec.: MH^+ = 346.

PREPARATIVE EXAMPLE 61

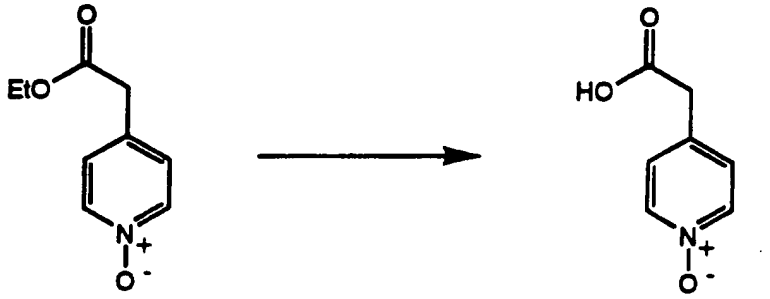


Step A:



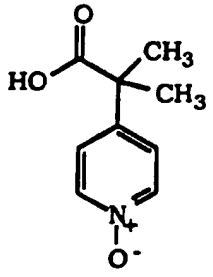
Combine 10 g (60.5 mmol) of ethyl 4-pyridylacetate and 120 mL of dry CH_2Cl_2 at -20°C, add 10.45 g (60.5 mmol) of MCPBA and stir at -20°C for 1 hour and then at 25°C for 67 hours. Add an additional 3.48 g (20.2 mmoles) of MCPBA and stir at 25°C for 24 hours. Dilute with CH_2Cl_2 and wash with saturated $NaHCO_3$ (aqueous) and then water. Dry over $MgSO_4$, concentrate *in vacuo* to a residue, and chromatograph (silica gel, 2%-5.5% (10% NH_4OH in MeOH)/CH_2Cl_2) to give 8.12 g of the product compound. Mass Spec.: MH^+ = 182.15

Step B:



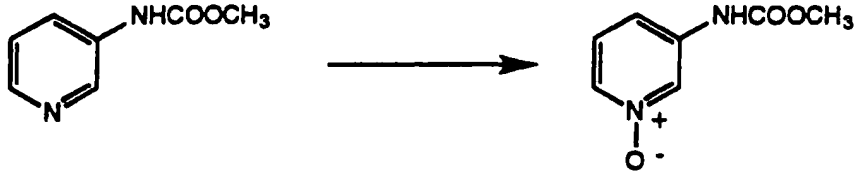
Combine 3.5 g (19.3 mmol) of the product of Step A, 17.5 mL of EtOH and 96.6 mL of 10% NaOH (aqueous) and heat the mixture at 67°C for 2 hours. Add 2 N HCl (aqueous) to adjust to pH = 2.37 and concentrate *in vacuo* to a residue. Add 200 mL of dry EtOH, filter through celite® and wash the filter cake with dry EtOH (2X50 ml). Concentrate the combined filtrates *in vacuo* to give2.43 g of the title compound.

Using the product of Preparative Example 26, of WO 95/10516, and substantially the same procedure as described for Preparative Example 61, Steps A and B, the following compound was prepared:



(61A)

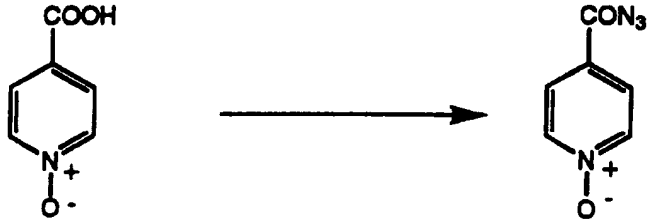
PREPARATIVE EXAMPLE 62



Combine 10 g (65.7 mmol) of 3-methoxycarbonylaminopyridine and 150 mL of CH_2Cl_2, cool to 0°C and slowly add (dropwise) a solution

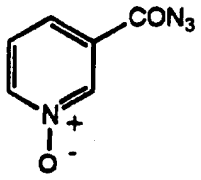
of 13.61 g (78.84 mmol) of MCPBA in 120 mL of CH_2Cl_2 at 0°C over a period of 1 hour. Stir the mixture at 25°C for 5 days, then wash with saturated $NaHCO_3$ (aqueous), then water and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2%-5% (10% NH_4OH in MeOH)/CH_2Cl_2) to give the product compound. Mass Spec.: MH^+ = 169

PREPARATIVE EXAMPLE 63



Combine 5 g (36.0 mmol) of isonicotinic acid 1-N-oxide and 150 mL of anhydrous DMF, add 5.5 mL (39.6 mmol) of Et_3N and stir at 0°C for 0.5 hours. Slowly add (dropwise) 8.5 mL (39.6 mmol) of diphenylphosphoryl azide at 0°C over 10 minutes, stir at 0°C for 1 hour and then at 25°C for 24 hours (as generally described in Pavia, *et al.*, Journal of Medicinal Chemistry, 33, 854-861 (1990). Concentrate *in vacuo* to a residue and chromatograph (silica gel, 0.5%-1% MeOH/CH_2Cl_2) to give 5.9 g of the product compound.

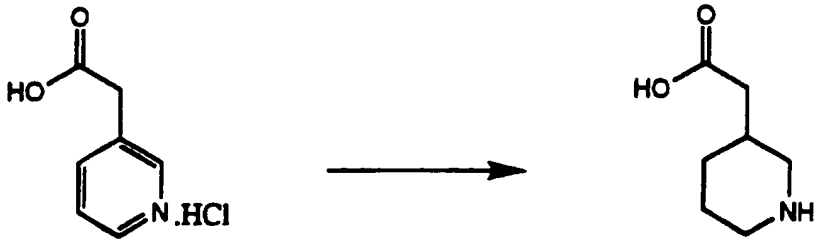
Using nicotinic acid 1-N-oxide and substantially the same procedure as described for Preparative Example 63 the following compound was prepared:



(63A)

PREPARATIVE EXAMPLE 64

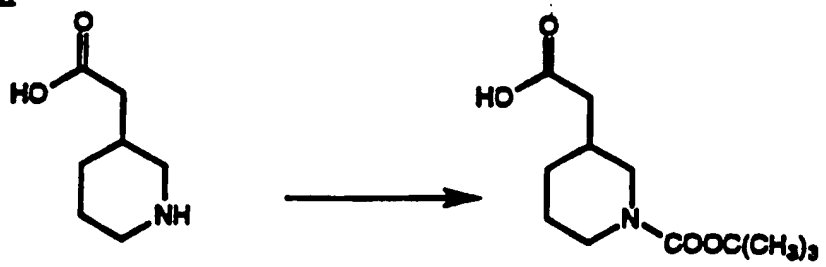
Step A:



Hydrogenate 25 g (144 mmol) of 3-pyridylacetic acid hydrochloride for 144 hours using the procedure described in Preparative Example 15,

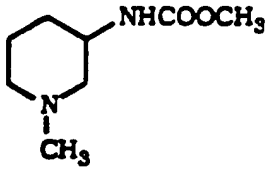
of WO 95/10516, to give 20 g of the product compound. Mass Spec.: MH^+ = 144.

Step B:



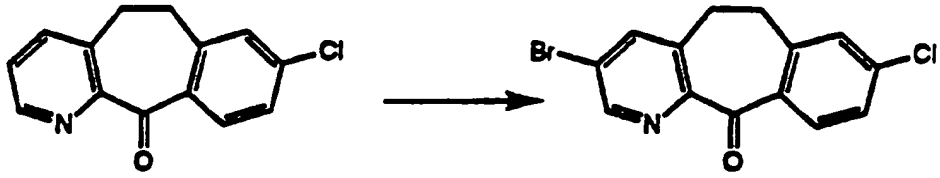
React 12 g (83.8 mmol) of the product of Step B for 148 hours using the procedure described in Preparative Example 13, Step B, of WO 95/10516, to give 17.5 g of the product compound. Mass Spec.: MH^+ = 244.25

PREPARATIVE EXAMPLE 65



Combine 25 g (164.4 mmol) of methyl 3-pyridylcarbamate and 163.3 mL of 1N HCl (aqueous), stir until all of the solid dissolves, then hydrogenate over 10% Pd/C at 25°C at 55 psi for 220 hours. Filter, wash the solids with water and treat the combined filtrates with 150 mL of BioRad AG1X8 ion exchange resin (OH^-). Filter, wash the resin with water and concentrate the filtrate to a volume of 100 mL. Add 16.43 mL (197.3 mmol) of 37% formalin and hydrogenate over 10% Pd/C at 25°C at 55 psi for 89 hours. Filter, wash the solids with water and concentrate *in vacuo* to give 24.3 g of the title compound. Mass Spec.: MH^+ = 173.2

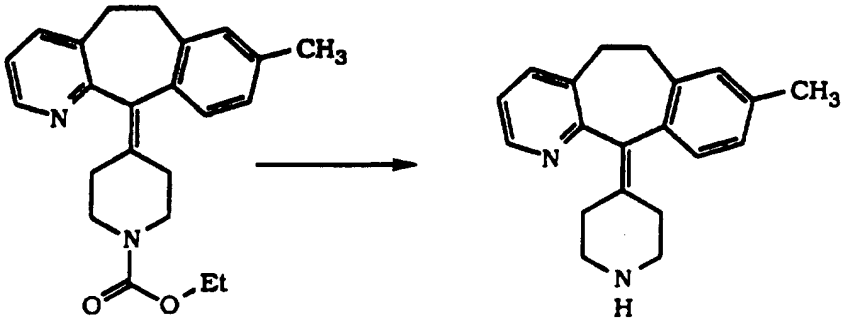
PREPARATIVE EXAMPLE 66



Cool 50.0 g (20.5 mmol) of 8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one to 0°C, slowly add 75 mL (93.69 mmol) of sulfur monochloride over 20 minutes, then slowly add 25 mL (48.59 mmol) of Br_2 over 15. Heat at 95°C for 20 hour, add 12.5 mL (24.3 mmol) of Br_2 and heat for a another 24 hours. Cool the mixture, and slowly add to a mixture of CH_2Cl_2 and 1N NaOH (aqueous) at 0°C. Wash

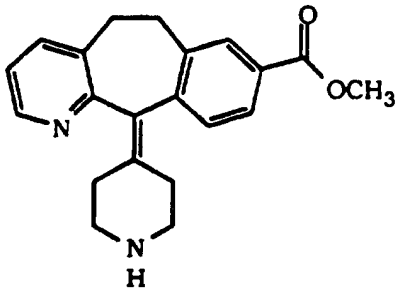
the organic phase with water, dry over $MgSO_4$ and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 500 mL CH_2Cl_2 then 0.2%-5% (10% NH_4OH in MeOH)/CH_2Cl_2), then chromatograph again (silica gel, 3%-8.5% EtOAc/hexane) to give 8.66 g of the product compound. Mass Spec.: $MH^+ = 322$

PREPARATIVE EXAMPLE 67

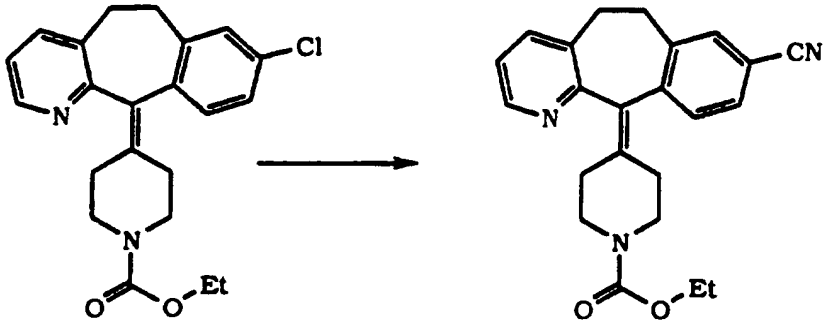


Dissolve 0.16 g (0.46 mmol) of 4-(8-methyl-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidine)-1-ethoxycarbonyl-piperidine, in 2 mL EtOH and add 4 mL of 12 N HCl. Heat the solution for 3 hours at 85°C, then cool to 25°C. Adjust to pH = 10 with 50% NaOH (aqueous) and extract several times with 50 mL of EtOAc. Combine the organic layers, dry them over $MgSO_4$, and concentrate *in vacuo* to give the product compound.

PREPARATIVE EXAMPLE 68

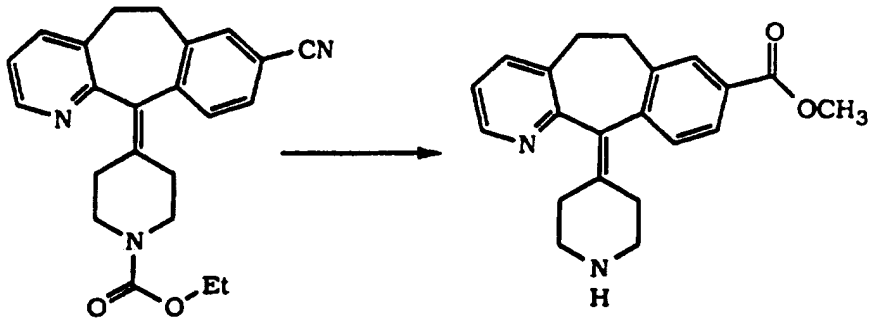


Step A:



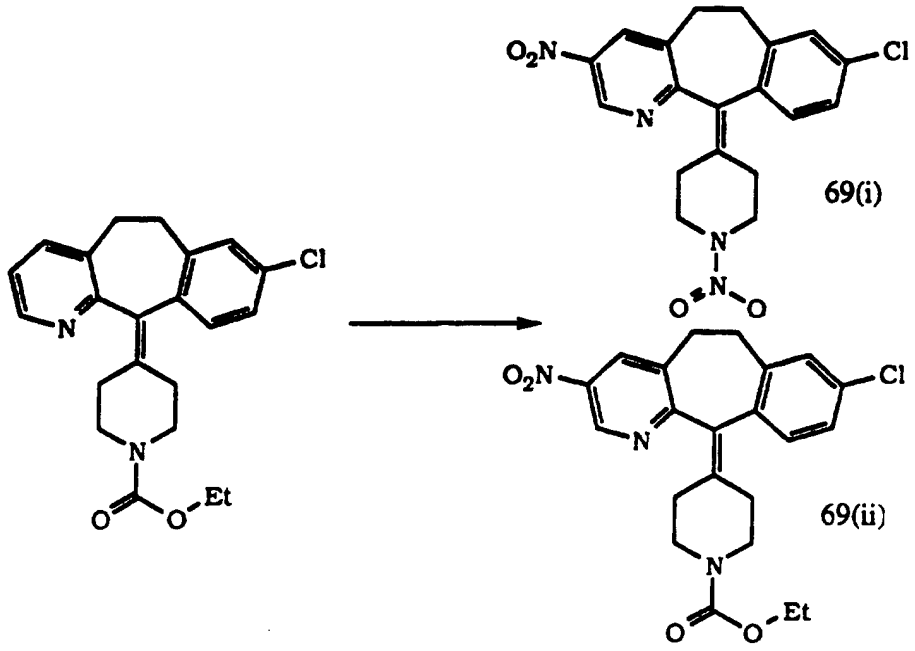
Disolve 2 g (5.22 mmol) of the title compound of Preparative Example 1F, of WO 95/10516, in 2.6 mL of dry N-methylpyrrolidinone. Add 0.87 g (9.4 mmol) of CuCN and 0.139 g (0.93 mmol) of sodium iodide. Heat the mixture at 200°C under nitrogen for 20 hours, cool to 25°C and repeatedly grind and mix with five 50 mL portions of CH_2Cl_2 and 7 M NH_4OH (aqueous). Wash the organic layer with 7 M NH_4OH until the organic layer is no longer blue or green. Dry the combined organic layers over $MgSO_4$ and concentrate *in vacuo* to a residue. Chromatograph (silica gel 70% EtOAc/hexane), then recrystallize from EtOAc/hexane to give the product compound. m.p. = 152.4°-153.5°C; Mass Spec.: MH^+ = 374

Step B:



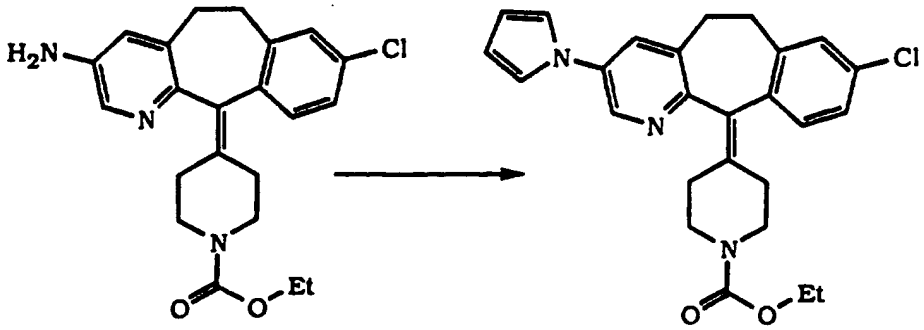
Dissolve 4.08 g (10.93 mmol) of the product of Step A in 12 M HCl and heat at 85°C for 18 hours. Concentrate *in vacuo* to a residue. Dissolve the residue in 175 mL of MeOH, saturate with HCl gas, and heat at reflux for 18 hours. Concentrate *in vacuo* to give the product compound as its HCl salt. Mass Spec.: MH^+ = 335

PREPARATIVE EXAMPLE 69



Combine 75 g (0.196 mole) of the Product of Example 1, Step F, of WO 95/10516, and 300 mL of CH_2Cl_2 at 0°C, and slowly add (dropwise) a solution of 72 g (0.236 mole) of tetrabutylammonium nitrate and 35 mL (0.247 mole) of TFAA in 500 mL of CH_2Cl_2. Stir at 25°C overnight, slowly add (dropwise) 1 L of saturated $NaHCO_3$ (aqueous). Separate the layers, wash the organic phase with brine and dry over $MgSO_4$. Concentrate *in vacuo* to a residue, chromatograph twice (1 kg silica gel, gradient of EtOAc/CH_2Cl_2) to give 8.63 g of product compound 69(i), and 34 g of product compound (ii). Recrystallize compound 69(i) from CH_2Cl_2/hexane to give the purified product compound 69(i). m.p.= 186°-187°C; Mass Spec.: (FAB) MH^+ = 401

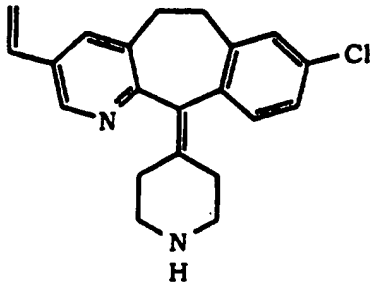
PREPARATIVE EXAMPLE 69A



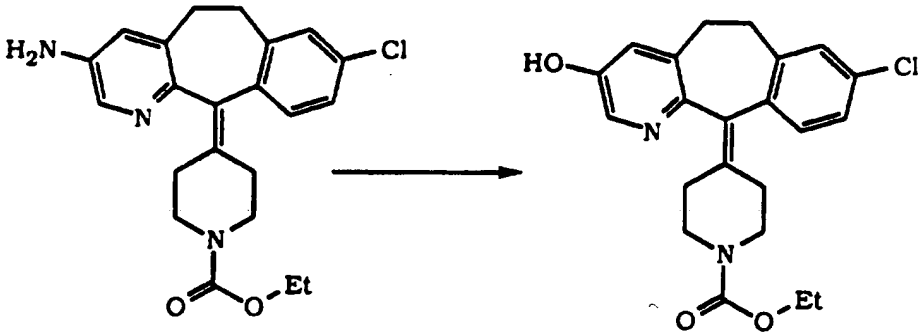
Combine 0.4 g (1 mmol) of the Product of Example 47, Step B, of WO 95/10516 (published April 20, 1995), and 0.2 mL (1.2 mmoles) of 2, 5-diethoxytetrahydrofuran in 3 mL of glacial HOAc, and heat at reflux for 1.5

hours. Cool the mixture, wash with saturated $NaHCO_3$ (aqueous), then with brine, dry over $MgSO_4$, and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 5%-15% EtOAc/CH_2Cl_2) to give 0.34 g of the product compound. Mass Spec.: (FAB) MH^+ = 448

PREPARATIVE EXAMPLE 70

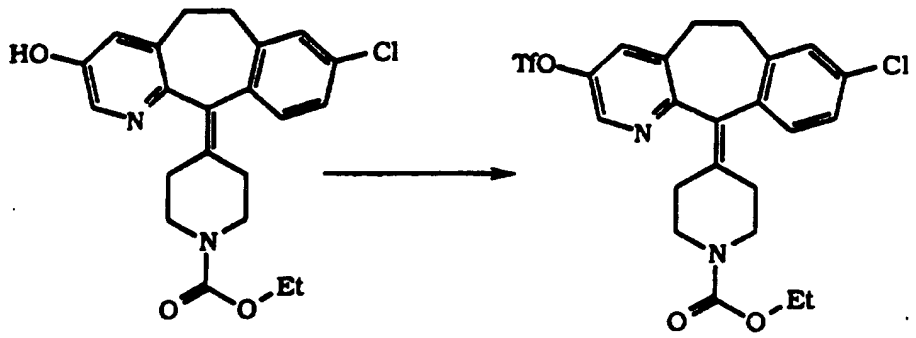


Step A:



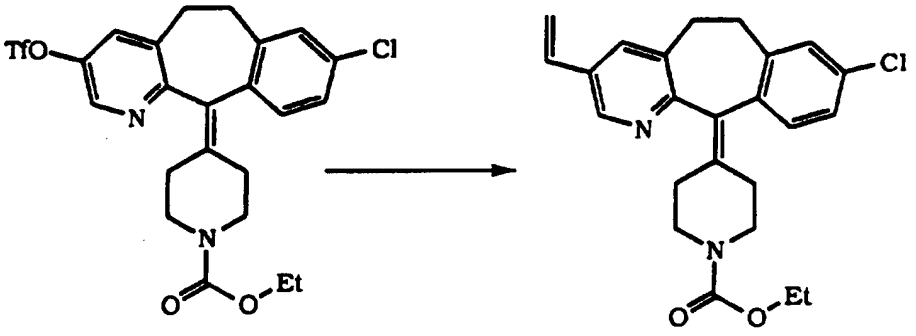
Combine 13.8 g (34.7 mmol) of the Product of Example 47, Step B, of WO 95/10516, and 90 mL of water at 0°C, add a solution of 6.9 mL of concentrated H_2SO_4 in 45 mL of water and stir the mixture. Slowly add (dropwise) a solution of 2.55 g (40 mmol) of $NaNO_2$ in 75 mL of water and stir at 0°-5°C for 0.5 hours. Add a boiling solution of 35.1 g $CuSO_4$ in 135 mL of water and heat at 100°C for 15 min. Cool the mixture, extract with CH_2Cl_2 (2 X 200 mL), wash the extracts with brine, dry over $MgSO_4$, and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 1.5%-10% MeOH/ CH_2Cl_2) to give 11.36 g of the product compound.

Step B:



Combine 11.36 g (28.5 mmol) of the Product of Step A and 12.4 g (34.7 mmol) of N-phenyltriflimide in 120 mL of dry CH_2Cl_2 at 0°C, add 4.6 mL (33 mmol) of Et_3N and stir at 25°C overnight. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2%-5% EtOAc/ CH_2Cl_2) to give 10.95 g of the product compound. Recrystallize from hot MeOH. m.p. = 154.5°-156°C; Mass Spec.: (FAB) MH^+ = 531

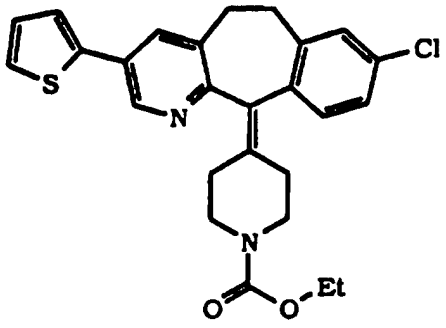
Step C:



Combine 12.2 g (23 mmol) of the Product of Step B and 85 mL of 1-methyl-2-pyrrolidinone at 25°C, then add 2.84 g LiCl, 0.212 g of tris-furylphosphine and 0.585 g of dipalladiumtribenzylideneacetone and stir for 15 min. Slowly add (dropwise) 7.5 mL (25.77 mmol) of tributylvinyltin and stir at 25°C for 2.5 hours. Dilute with 500 mL of water at 0°C and extract with 6700 mL of EtOAc. Filter the organic phase through celite®, wash the celite with EtOAc, then wash the filtrate twice with 30% NaF (aqueous). Filter the organic solution, wash with brine and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 15%-40% EtOAc/hexane) to give 8.58 g of the product compound. Mass Spec.: (FAB) MH^+ = 409

Using 2-(tributylstannyl)thiophene and the compound of Preparative Example 70, Step B, and following substantially the same

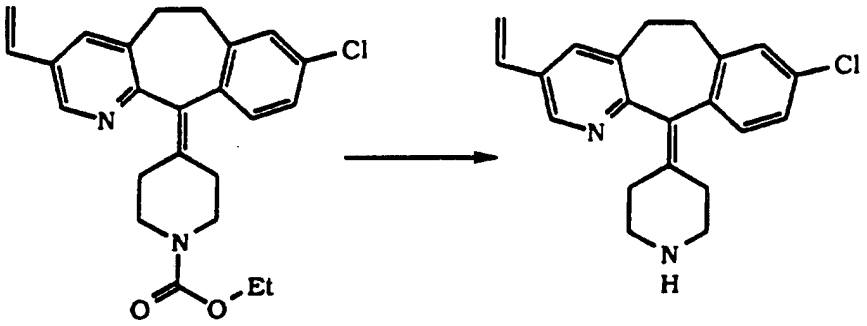
procedure as described for Preparative Example 70, Step C, the compound:



(Preparative Example 70-A)

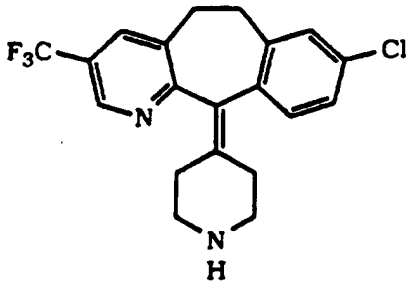
was prepared. m.p. = 155°-157°C, Mass Spec.: MH^+ = 465.

Step D:

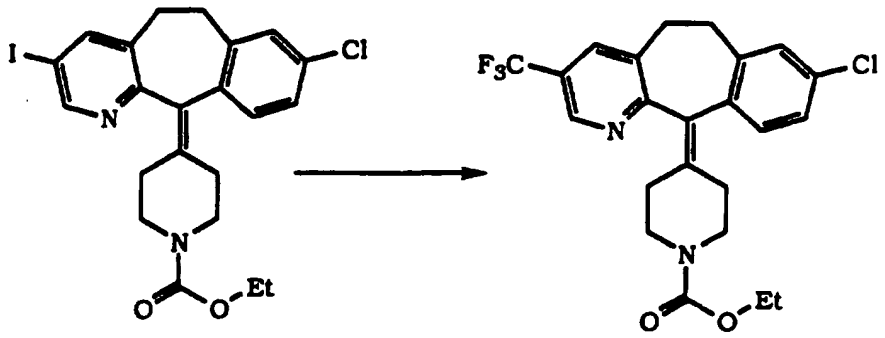


Hydrolyze 1.18 g (2.89 mmol) of the product of Step C via substantially the same procedure as described in Example 358, Step A, of WO 95/10516 ,to give 0.95 g of the product compound. Mass Spec.: (FAB) MH^+ = 337

PREPARATIVE EXAMPLE 71

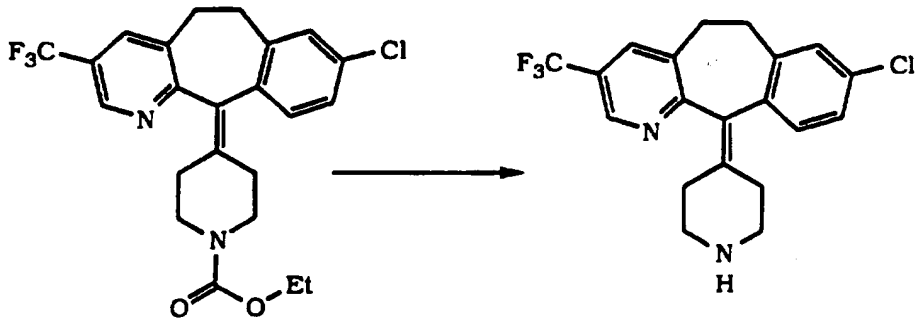


Step A:



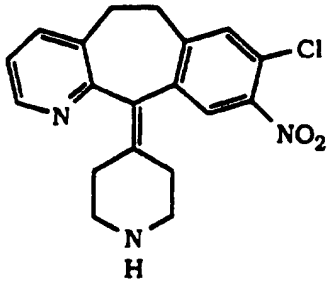
Combine 1.01 g (19.9 mmol) of the Product of Preparative Example 48, Step A, 30 mL of DMF, 1.33 g (6.96 mmol) of methyl 2,2-difluoro-2-(fluorosulfonyl)-acetate and 0.75 g (3.97 g) of CuI. Heat the mixture at 60°-80°C for 3 hours, then concentrate to a residue. Dilute the residue with water, extract with CH_2Cl_2, and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 30% EtOAc/hexane, then 10% MeOH/CH_2Cl_2 + NH_4OH) to give 0.15 g of the product compound. Mass Spec.: MH^+ = 451.1

Step B:

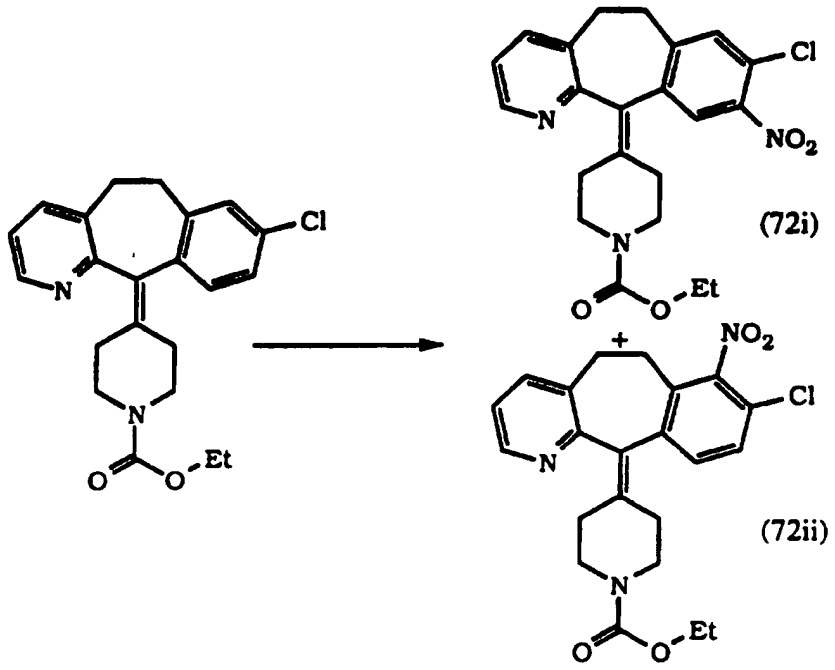


Hydrolyze the product of Step A using essentially the same procedure as described in Preparative Example 1, Step G, of WO 95/10516, to give the product compound. Mass Spec.: MH^+ = 379

PREPARATIVE EXAMPLE 72

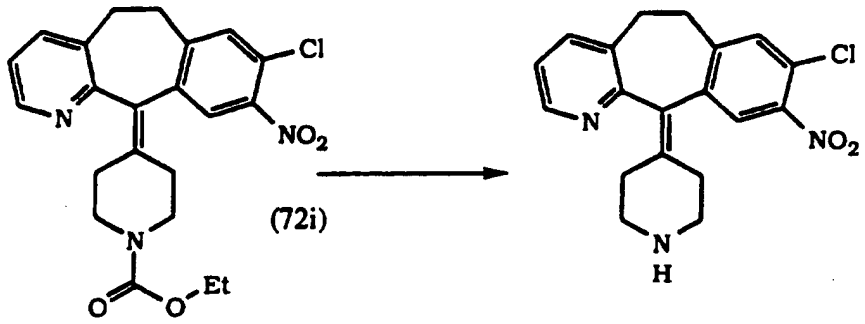


Step A:



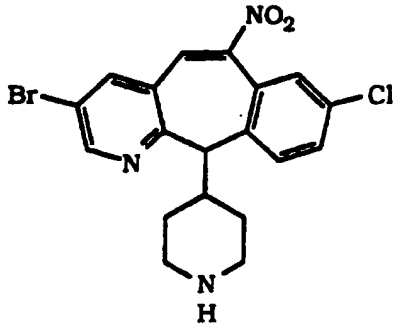
Dissolve 20 g (50 mmol) of the Product of Preparative Example 1, Step F, of WO 95/10516, in 400 mL of concentrated H_2SO_4, cool to -5°C and add 5.1 g (50 mmol) of KNO_3 in small portions. Stir for 3 hours, cool the mixture and slowly basify with 50% NaOH (aqueous). Extract with CH_2Cl_2 (3 X 500 mL), dry the combined extracts over $MgSO_4$, and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 50% EtOAc/hexane) to give 16.33 g of the product compound (72i) and 2.6 g of the product compound (72ii). Mass Spec. (72(i) and (72(ii)): MH^+ = 428

Step B:

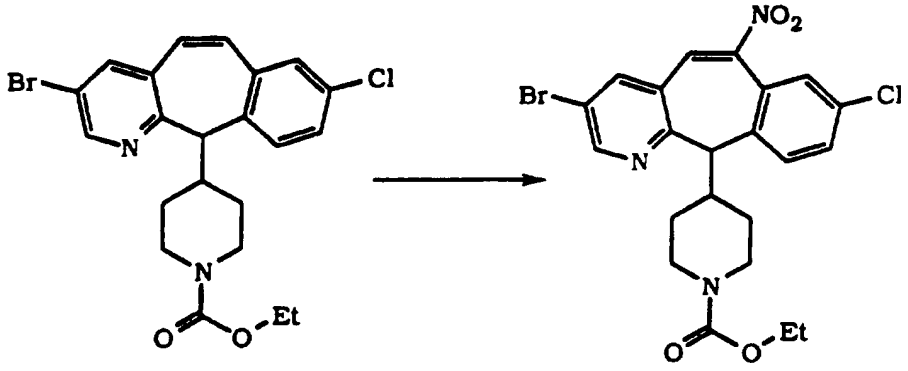


Hydrolyze 5.46 g (12.76 mmol) of the Product of (72i) from Step A, via substantially the same procdure as described for Example 358, Step A, of WO 95/10516, to give 4.34 g of the product compound. Mass Spec.: MH^+ = 356

PREPARATIVE EXAMPLE 73

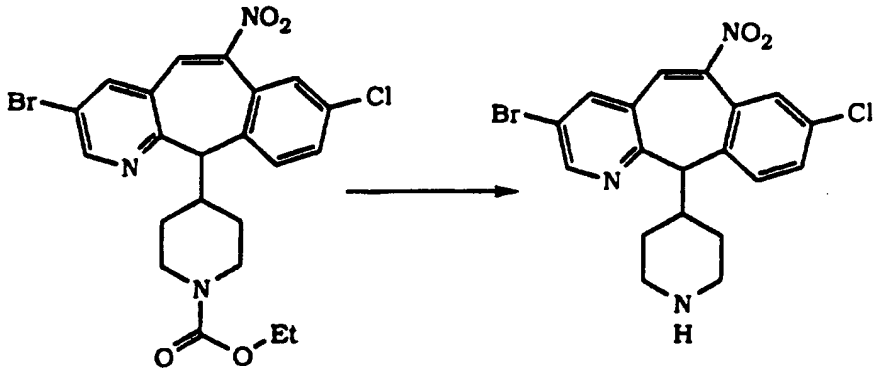


Step A:



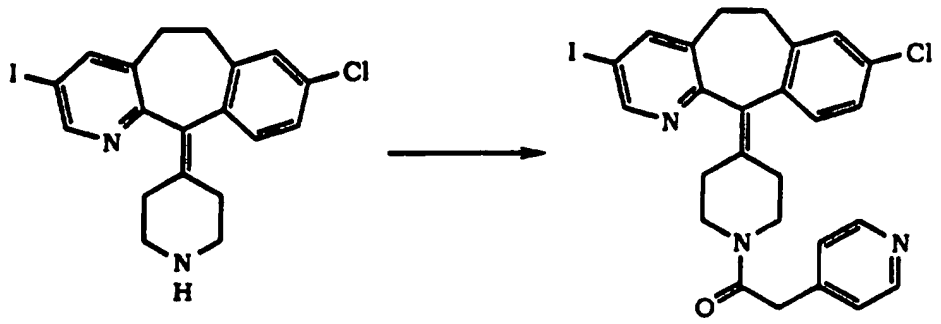
Combine 1.6 g of the Product (54i) of Preparative Example 54, Step B, 12 mL of CH_2Cl_2, and 1.16 g of tetrabutylammonium nitrate, cool to 0°C and slowly add (dropwise) a solution of 0.8 g of TFAA in 2 mL of CH_2Cl_2. Stir for 6 hours at 0°C, let the mixture stand at 0°C overnight, then wash successively with saturated $NaHCO_3$ (aqueous), water and brine, and dry over Na_2SO_4. Concentrate *in vacuo* to a residue, then chromatograph (silica gel, 30% EtOAc/hexane) to give 0.38 g of the product compound.

Step B:



Hydrolyze 0.38 g of the Product of Step A via substantially the same procedure as described for Example 358, Step A, of WO 95/10516, to give 0.235 g of the product compound.

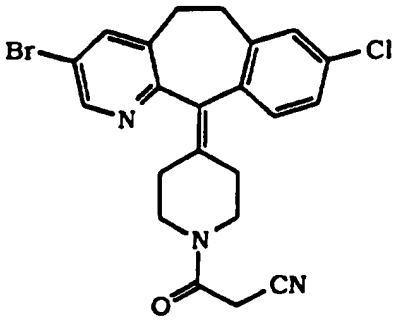
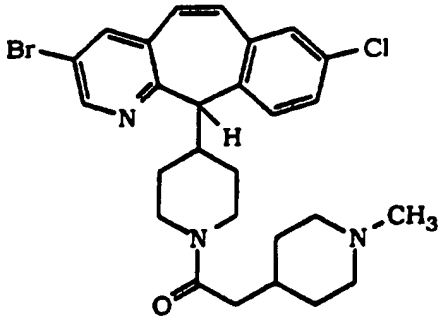
EXAMPLE 400

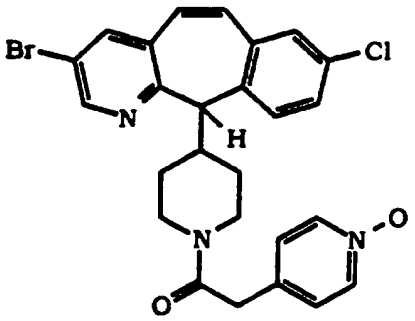
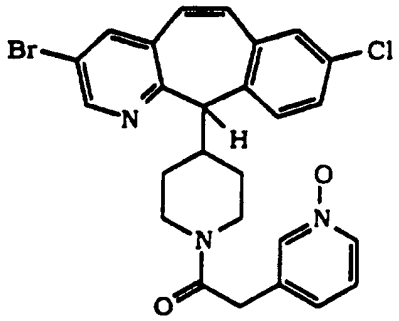
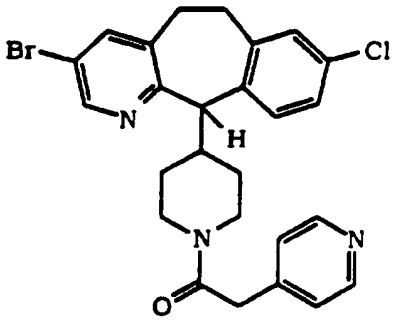
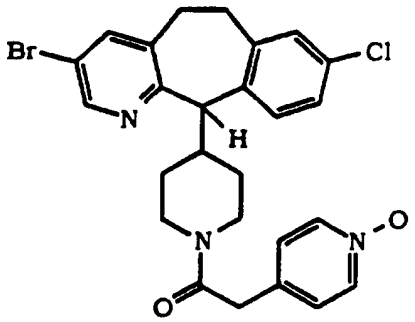


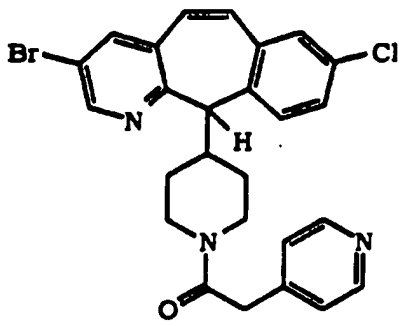
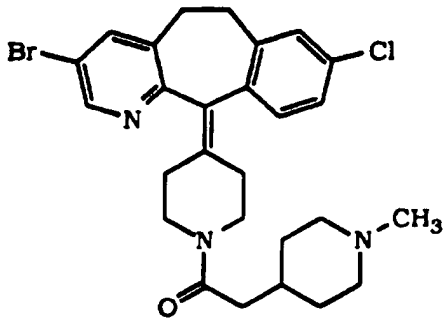
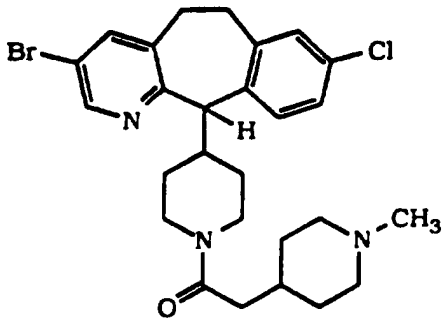
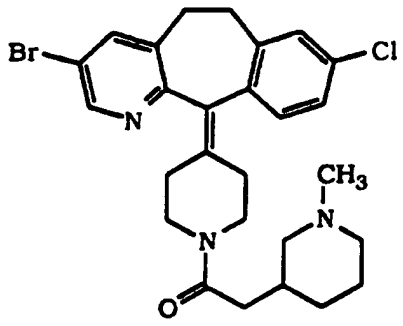
The product of Preparative Example 48, Step B, is reacted with 4-pyridyl acetic acid via essentially the same procedure as described in Example 180, of WO 95/10516, to give the product compound (5.210). Mass Spec.: $MH^+ = 556$

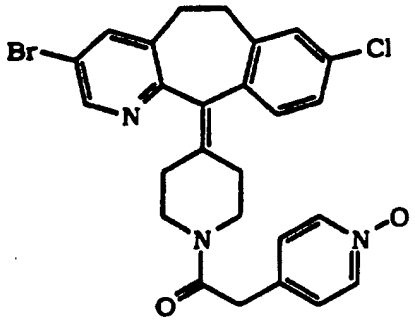
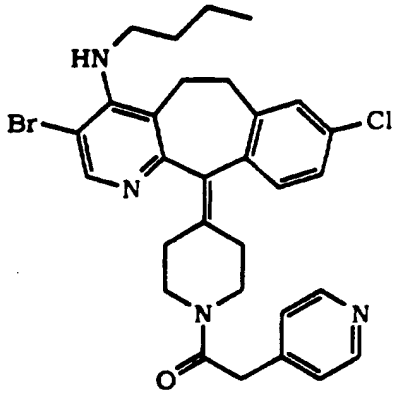
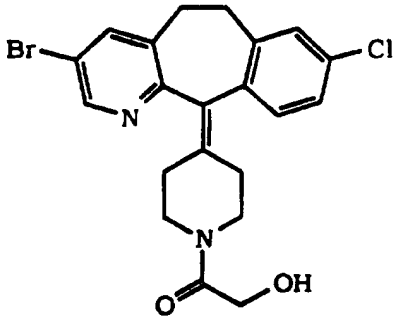
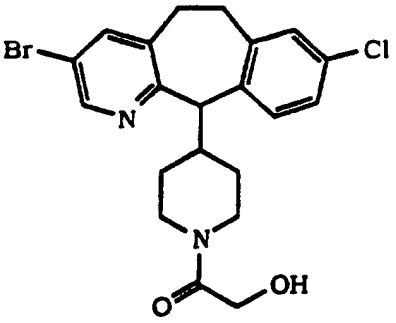
Using the appropriate carboxylic acid and the starting compound indicated, the compounds in Table 2 were prepared via substantially the same procedure as described for Example 400:

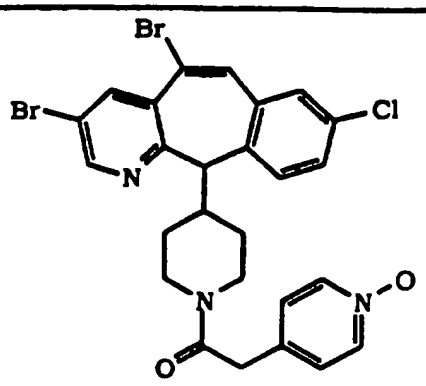
TABLE 2

Starting Compound	Product Compound	Analytical Data
Preparative Example 49	 Example 400-A	Mass Spec: $MH^+ = 458$
Preparative Example 53C	 Example 400-B (5.203)	Mass Spec.: $MH^+ = 528.2$

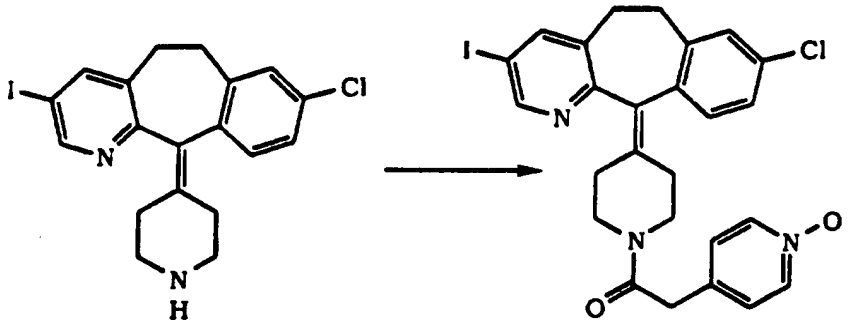
Preparative Example 53C	 Example 400-C (5.200)	Mass Spec.: MH^+ = 524.2
Preparative Example 53C	 Example 400-D (5.217)	Mass Spec.: MH^+ = 524.1
Preparative Example 51A	 Example 400-E (5.208)	Mass Spec.: MH^+ = 512.1
Preparative Example 51A	 Example 400-F (5.201)	Mass Spec.: MH^+ = 528

Preparative Example 53C	 Example 400-G (5.204)	Mass Spec.: MH^+ = 508.0
Preparative Example 49	 Example 400-H (5.220)	Mass Spec.: MH^+ = 530.2
Preparative Example 51A	 Example 400-J (5.212)	Mass Spec.: MH^+ = 532.3
Preparative Example 49	 Example 400-K (5.218)	Mass Spec.: MH^+ = 530.2

Preparative Example 49	 Example 400-L (5.206)	Mass Spec.: MH^+ = 526
Preparative Example 56, Step C	 Example 400-M	Mass Spec.: MH^+ = 581
Preparative Example 49	 Example 400-N	Mass Spec.: MH^+ = 449.2
Preparative Example 51A	 Example 400-P	m.p. = 62.8°-63.5°C Mass Spec.: MH^+ = 451

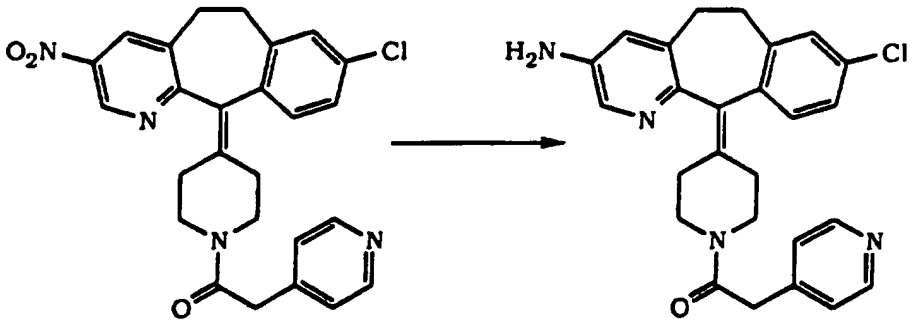
Preparative Example 53B	 Example 400-Q	Mass Spec.: MH^+ = 602

EXAMPLE 401



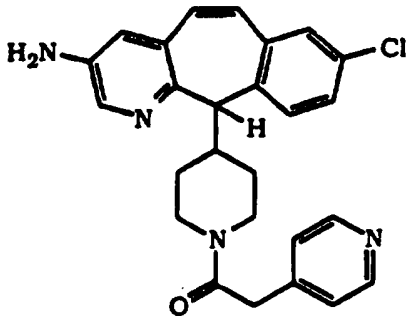
The product of Preparative Example 48, Step B, is reacted with 4-pyridyl acetic acid N-oxide via essentially the same procedure as described in Example 227 to give the product compound (5.209). Mass Spec.: MH^+ = 572

EXAMPLE 402



The product of Example 358, Step B, of WO 95/10516, is reduced via essentially the same procedure as described in Step B of Preparative Example 47, of WO 95/10516, to give the product compound. mp=133.2-133.4 °C MH^+ 445

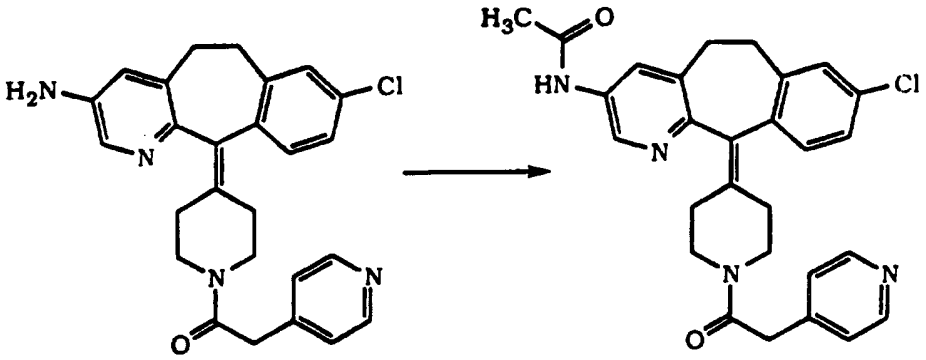
Using the compound of Example 411-B, and following substantially the same procedure as described for Example 402, the compound:



(Example 402-A)

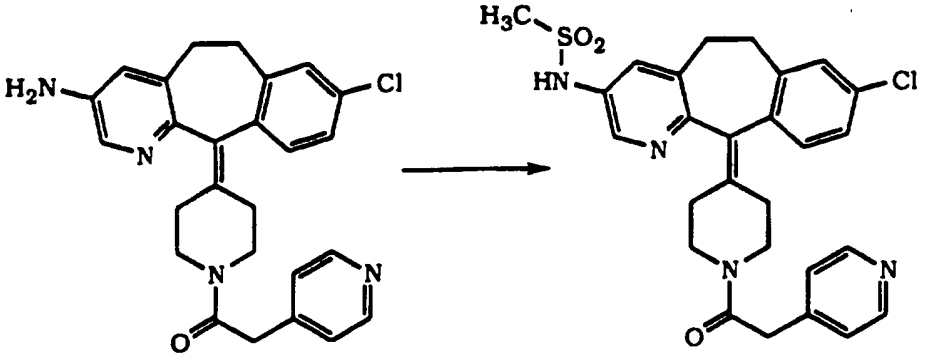
was prepared. Mass Spec.: MH^+ = 445.2

EXAMPLE 403



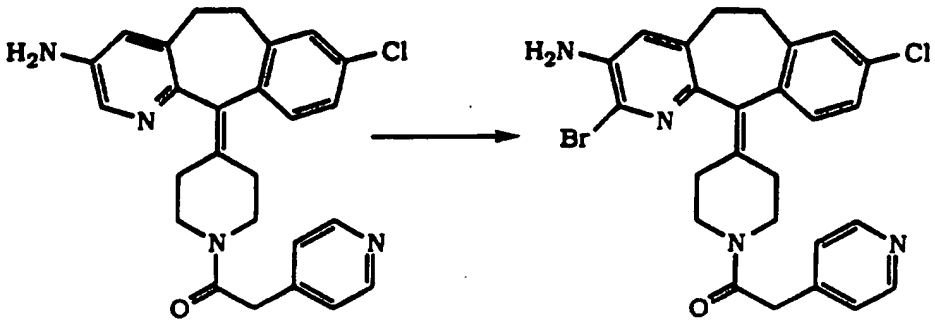
Combine 0.3 g (0.67 mmol) of the product of Example 402, 5 mL of pyridine and 0.1 g (1.01 mmol) of acetic anhydride and stir the mixture at room temperature for 2 days. Add another 100 µL of acetic anhydride, warm to 60°C and stir for 6h. Neutralize the reaction mixture then basify with 1 N NaOH (aqueous) to pH =10. Extract with CH_2Cl_2, dry the extract over $MgSO_4$ and concentrate to a residue. Purify the residue by HPLC eluting 8% MeOH/CH_2Cl_2 + concentrated NH_4OH (aqueous) to give 0.22 g of the product compound. Mass Spec.: MH^+ = 487

EXAMPLE 404



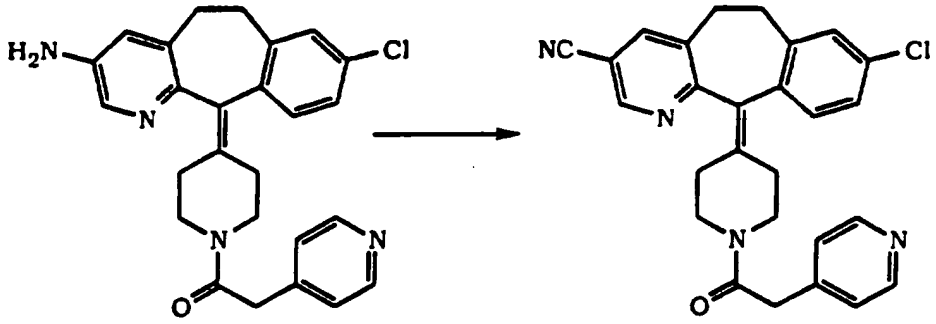
The product of Example 402 is reacted with methanesulfonyl chloride via substantially the same procedure as described for Example 403 to give the 0.32 g of the product compound. Mass Spec.: MH^+ = 523

EXAMPLE 405



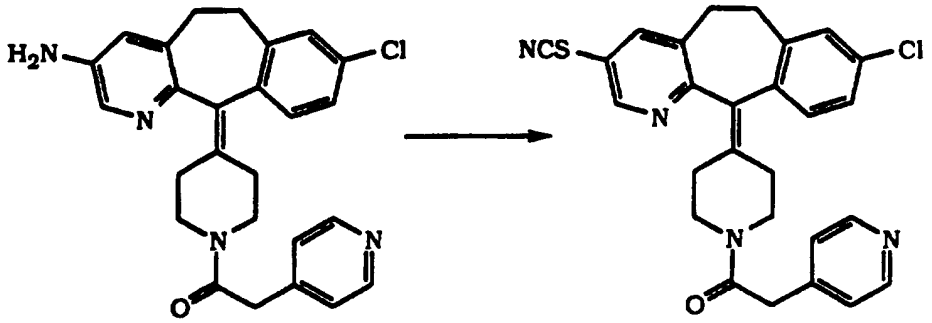
Combine 1.5 g (3.37 mmol) of the product of Example 402 and 10 mL of AcOH, then add 3.37 mL of a solution of bromine in AcOH and stir the mixture at room temperature overnight. Basify the mixture with 1N NaOH (aqueous) to basic pH, then extract with EtOAc. Concentrate the extract to a residue and chromatograph (silica gel, 90% EtOAc/hexane, then 5% Et_3N/EtOAc) to give the product compound. Mass Spec.: MH^+ = 525.

EXAMPLE 406



Combine 0.5 g (1.12 mmol) of the product of Example 402 and 10 mL of acetone, add 230 µL of conc. HCl (aqueous) and 4 mL of water, and cool to -10°C. Add a solution of 0.085 g $NaNO_2$ in 4 mL of water, stir for 15 min., then add the reaction mixture to a solution of CuCN [freshly prepared by adding 0.336 g (1.34 mmol) of $CuSO_4$ in 2 mL of water to H_2O a solution of 0.365 g (5.6 mmol) of KCN in 2 mL of H_2O]. Heat the mixture to 60°-70°C, then at 70°-80°C to remove acetone. Cool the mixture and dilute with H_2O, then exhaustively extracted with CH_2Cl_2. Concentrate the extracts to a residue then purify by HPLC using 3 % methanolic ammonia in CH_2Cl_2 to give 0.25 g (50% yield) of the product compound. Mass Spec.: MH^+ = 455.

EXAMPLE 407

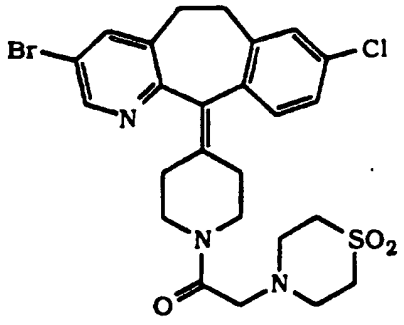


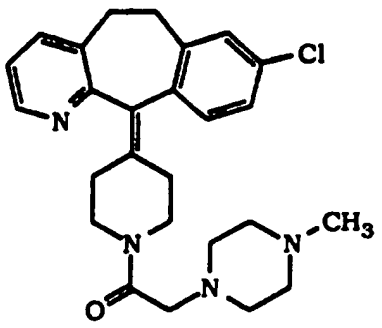
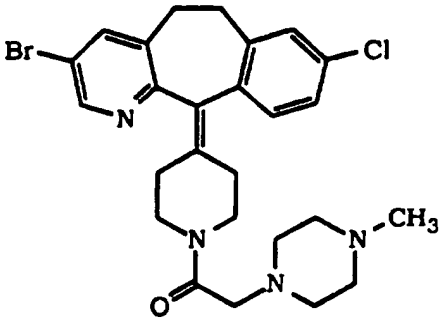
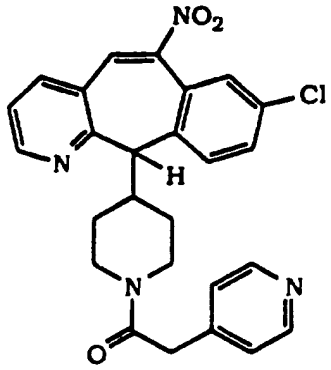
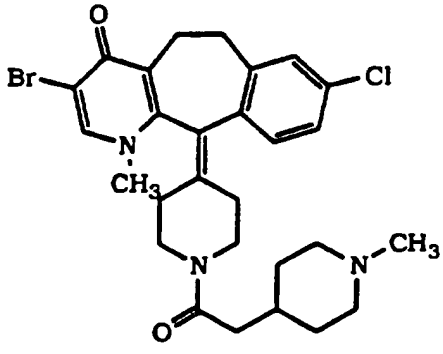
Combine 0.55 g (1.25 mmol) of the product of Example 402 and 50 mL of dilute H_2SO_4 at room temperature. Cool the mixture to -10°C, add a solution of 0.092 g of $NaNO_2$ in 5 mL of water was added and stir for 15 min. Slowly add a solution of 0.46 g (4.7 mmol) of KSCN and 0.3 g (2.49 mmol) of CuSCN in 15 mL of water over a period of 0.5 hours. Stir for 0.5 hour then heat at reflux for 15 min. Cool the mixture and adjust the pH to ~7, then extract with CH_2Cl_2. Concentrate the extracts to a residue and chromatograph (silica gel, 3% MeOH/CH_2Cl_2 + NH_4OH) to give the product compound. Mass Spec.: MH^+ = 487

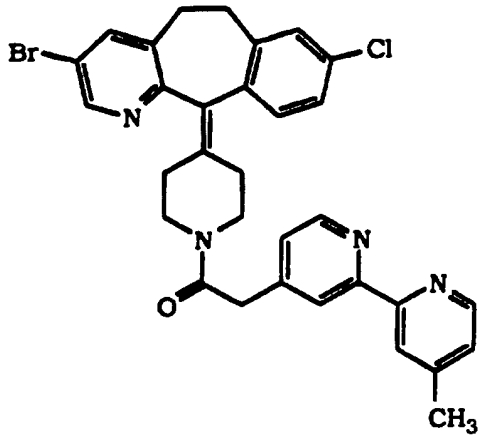
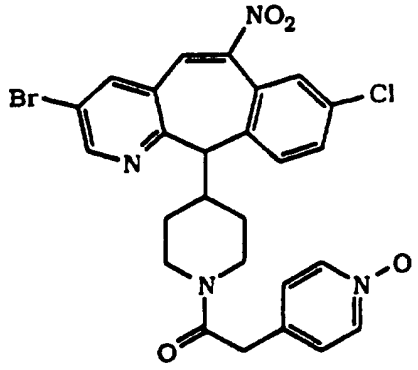
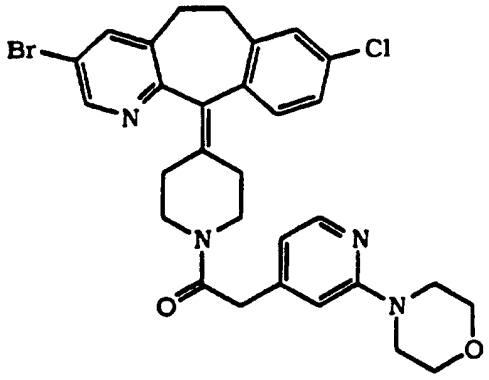
EXAMPLE 410

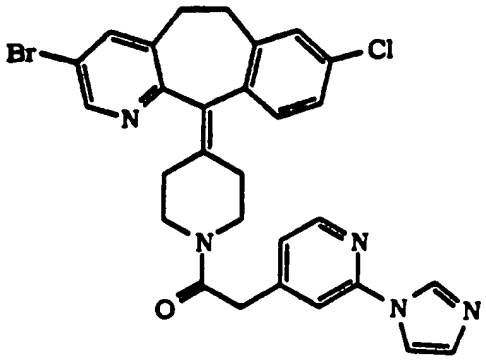
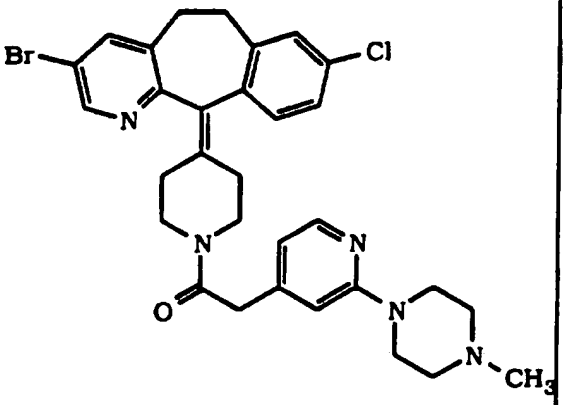
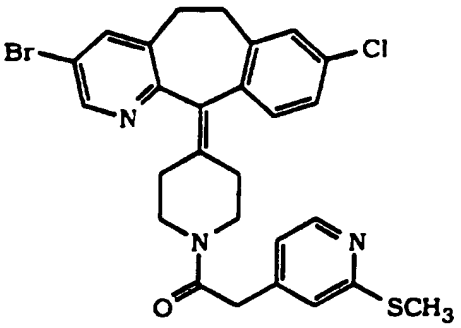
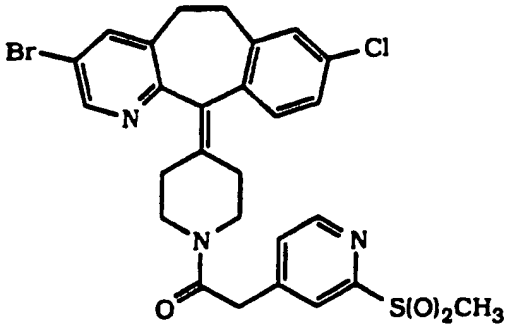
Using the appropriate carboxylic acid and the starting compound indicated, the compounds in Table 3 were prepared via substantially the same procedure as described in Example 180 of of WO 95/10516:

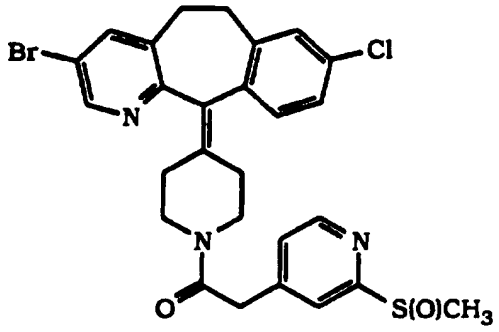
TABLE 3

Starting Compound	Product Compound	Analytical Data
Preparative Example 49	 Example 410-G	m.p. = 137°-138°C Mass Spec.: MH^+ = 565

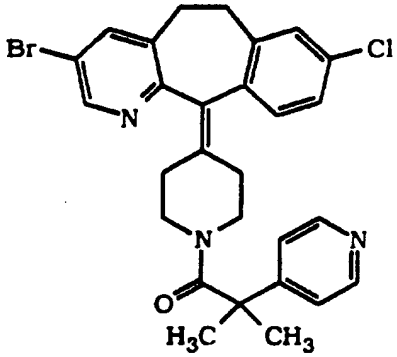
Preparative Example 1 of WO 95/10516	 Example 410-H	Mass Spec.: MH^+ = 451.2
Preparative Example 49	 Example 410-J	Mass Spec.: MH^+ = 531.2
Preparative Example 53	 Example 410-L	Mass Spec.: MH^+ = 475.2
Preparative Example 57	 Example 410-M	m.p. = 151°-153°C Mass Spec.: MH^+ = 560

Preparative Example 49	 Example 410-Q	m.p. = 102.6°-103°C Mass Spec.: MH^+ = 601.2
Preparative Example 73	 Example 410-R	Mass Spec.: MH^+ = 569
Preparative Example 49	 Example 410-S	m.p. = 97°C (dec.) Mass Spec.: MH^+ = 595

Preparative Example 49	 Example 410-T	m.p.= 132.6°C (dec.) Mass Spec.: MH^+ = 576
Preparative Example 49	 Example 410-U	m.p.= 111.2°C (dec.) Mass Spec.: MH^+ = 608
Preparative Example 49	 Example 410-V	m.p.= 85.1°C (dec.) Mass Spec.: MH^+ = 556
Preparative Example 49	 Example 410-W	m.p.= 114°C (dec.) Mass Spec.: MH^+ = 588

Preparative Example 49	 Example 410-X	m.p.= 122.5°-126.0°C Mass Spec.: MH^+ = 572

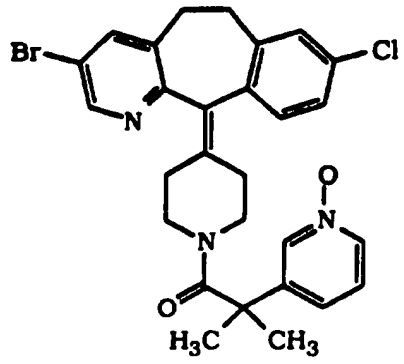
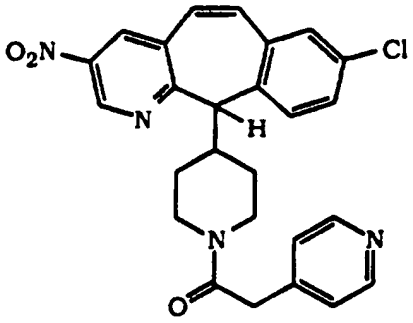
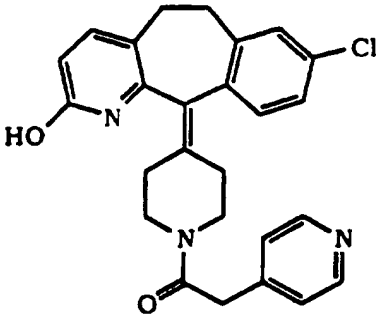
EXAMPLE 411

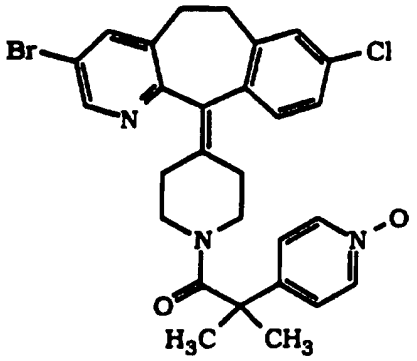
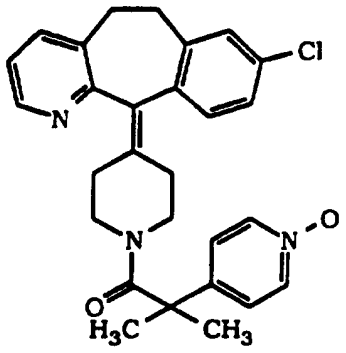
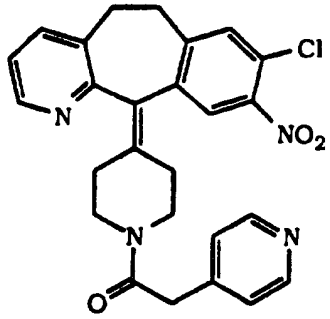
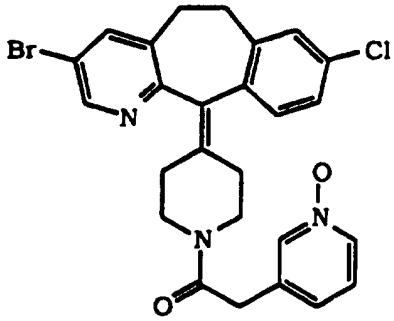


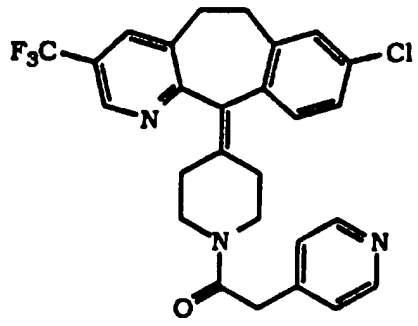
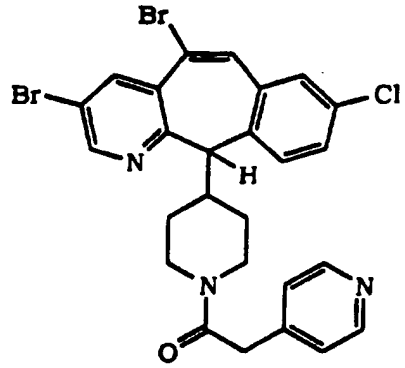
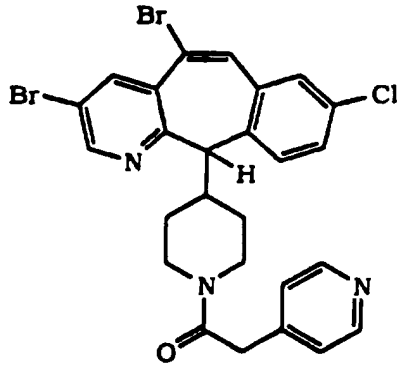
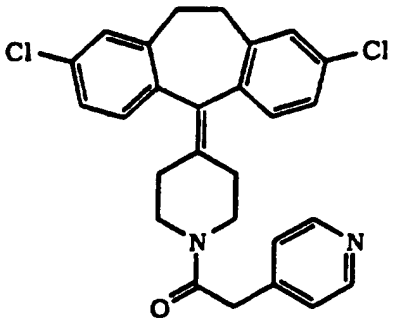
The product of Preparative Example 49 was reacted with 2-methyl-2-(4-pyridyl)propanoic acid via substantially the same procedure as described for Example 180, of WO 95/10516, to give the product compound. Mass Spec.: MH^+ = 538

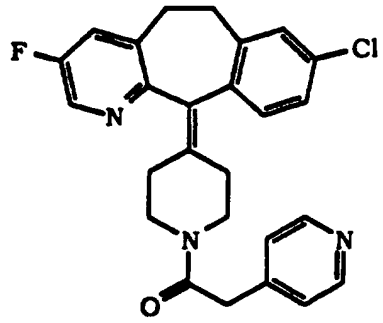
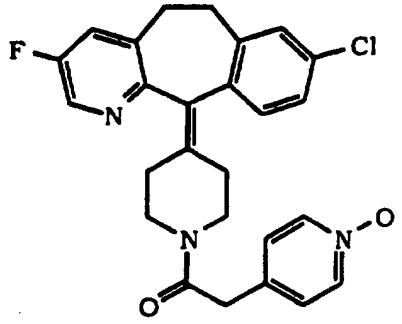
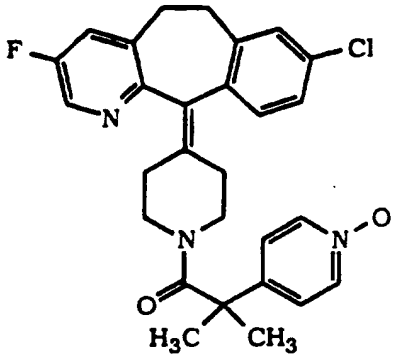
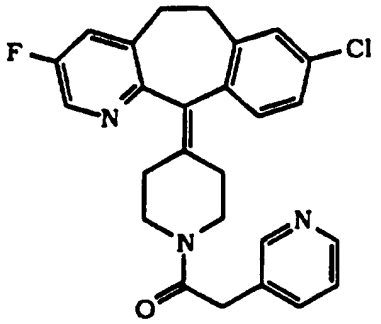
Using the appropriate carboxylic acid (or carboxylate salt, e.g. lithium carboxylate) and the starting compound indicated, the compounds in Table 4 were prepared via substantially the same procedure as described for Example 410:

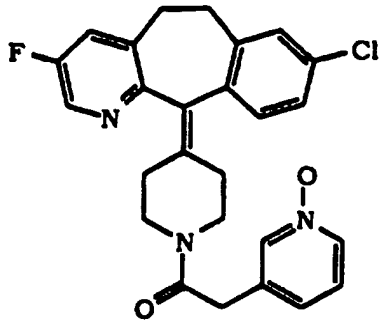
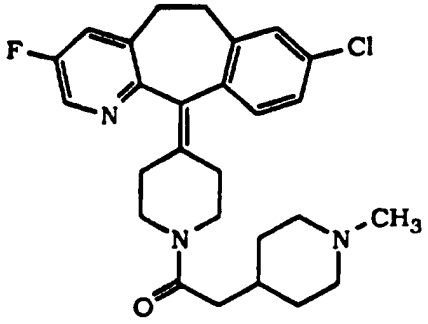
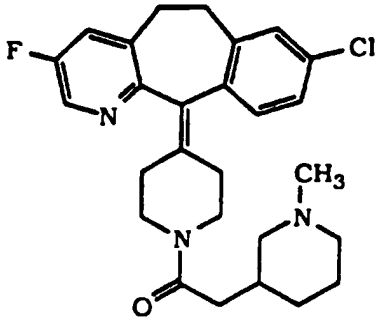
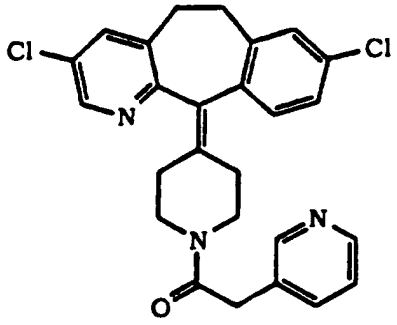
TABLE 4

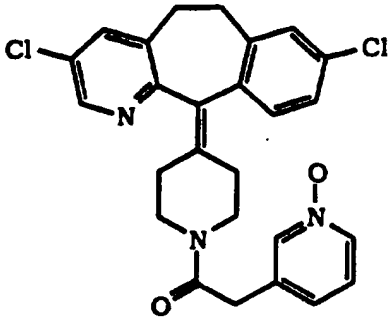
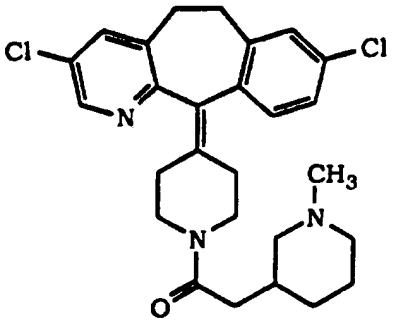
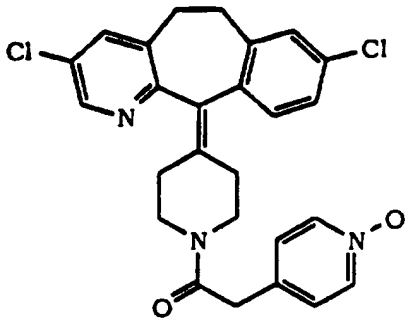
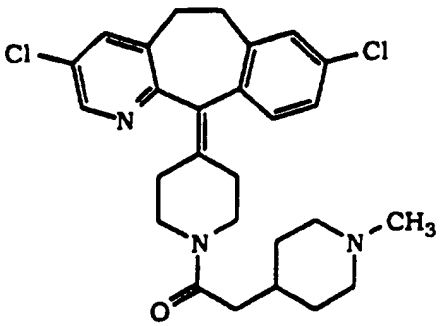
Starting Compound	Product Compound	Analytical Data
Preparative Example 49	 Example 411-A	Mass Spec.: MH^+ = 554
Preparative Example 53A	 Example 411-B	Mass Spec.: MH^+ = 475.2
Preparative Example 55	 Example 411-C	m.p. = 155.2°-158.9°C Mass Spec.: MH^+ = 446

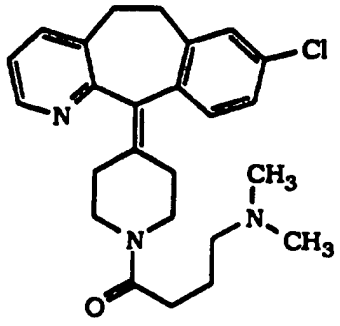
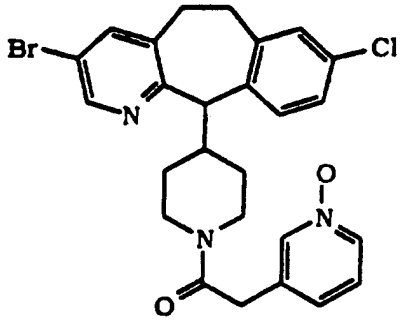
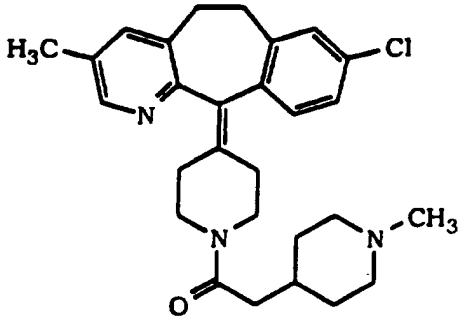
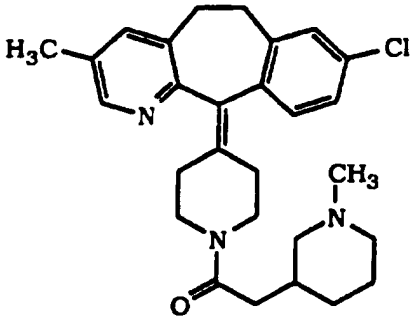
Preparative Example 49	 Example 411-D	Mass Spec.: MH^+ = 554
Preparative Example 1 of WO 95/10516	 Example 411-E	Mass Spec.: MH^+ = 474
Preparative Example 72	 Example 411-F	Mass Spec.: MH^+ = 475
Preparative Example 49	 Example 411-G	Mass Spec.: MH^+ = 526.1

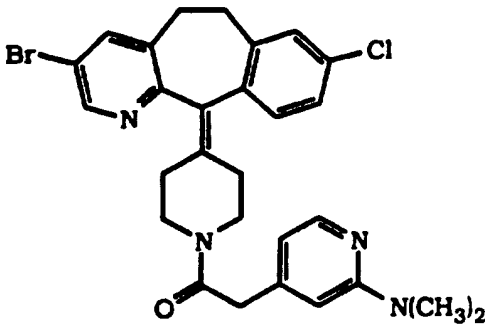
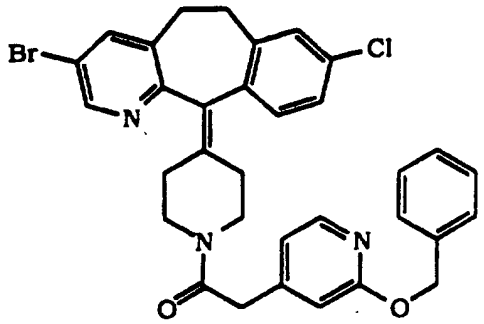
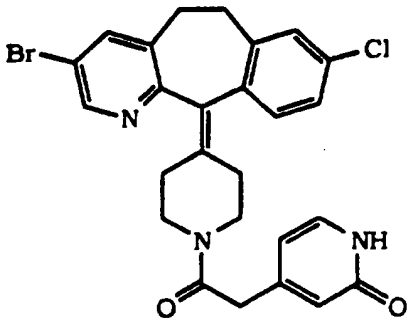
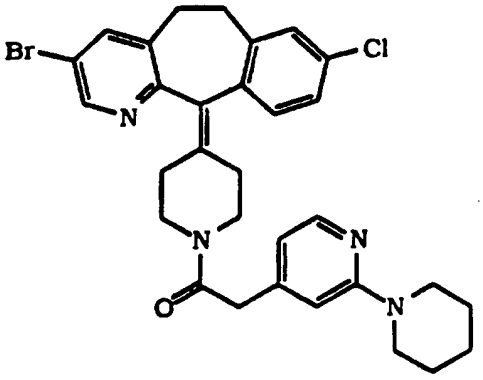
Preparative Example 71	 Example 411-H	Mass Spec.: MH^+ = 498
Preparative Example 53B	 Example 411-J	Mass Spec.: MH^+ = 536
Preparative Example 53B	 Example 411-K	Mass Spec.: MH^+ = 581
Preparative Example 59	 Example 411-L	m.p. = 97°-98°C Mass Spec.: (FAB) MH^+ = 463.1

Preparative Example 60	 Example 411-M	Mass Spec.: MH^+ = 448
Preparative Example 60	 Example 411-N	Mass Spec.: MH^+ = 464
Preparative Example 60	 Example 411-O	Mass Spec.: MH^+ = 492
Preparative Example 60	 Example 411-P	Mass Spec.: MH^+ = 448

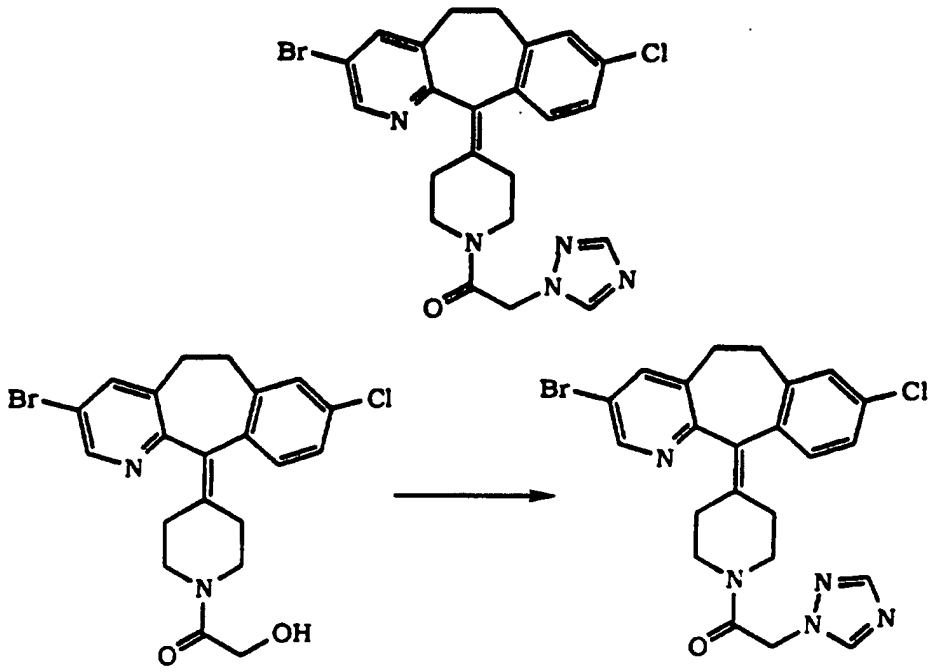
Preparative Example 60	 Example 411-Q	Mass Spec.: MH^+ = 464
Preparative Example 60	 Example 411-R	Mass Spec.: MH^+ = 469
Preparative Example 60	 Example 411-S	Mass Spec.: MH^+ = 469
Preparative Example 60A	 Example 411-T	Mass Spec.: MH^+ = 465

Preparative Example 60A	 Example 411-U	Mass Spec.: MH^+ = 481
Preparative Example 60A	 Example 411-V	Mass Spec.: MH^+ = 485
Preparative Example 60A	 Example 411-W	Mass Spec.: MH^+ = 481
Preparative Example 60A	 Example 411-X	Mass Spec.: MH^+ = 485

Preparative Example 1 Step G of WO 95/10516	 Example 411-Z	-----
Preparative Example 51A	 Example 411-AA	m.p. = 125°-125.4°C Mass Spec.: MH^+ = 528
Preparative Example 3 Step E of WO 95/10516	 Example 411-BB	m.p. = 186.6°-187°C Mass Spec.: MH^+ = 464
Preparative Example 3 Step E of WO 95/10516	 Example 411-CC	Mass Spec.: MH^+ = 464

Preparative Example 49	 Example 411-DD	m.p. = 80.2°C (dec.) Mass Spec.: MH^+ = 553
Preparative Example 49	 Example 411-EE	m.p. = 83°-86°C Mass Spec.: MH^+ = 616
Preparative Example 49	 Example 411-FF	m.p. = 167°-171°C Mass Spec.: MH^+ = 526
Preparative Example 49	 Example 411-GG	m.p. = 134°-140°C Mass Spec.: MH^+ = 593

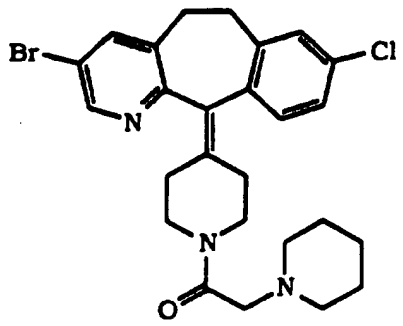
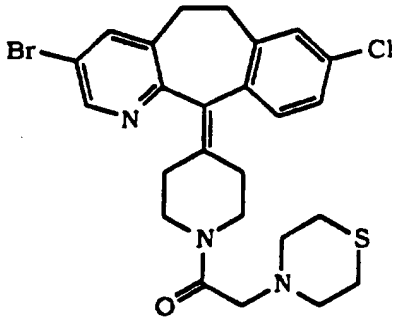
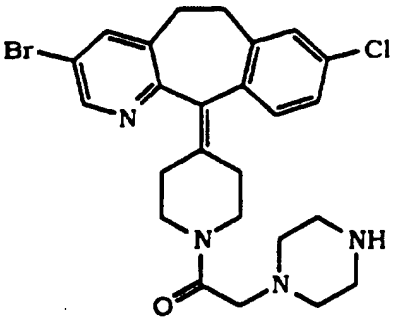
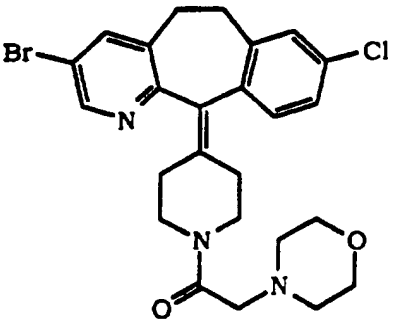
EXAMPLE 412

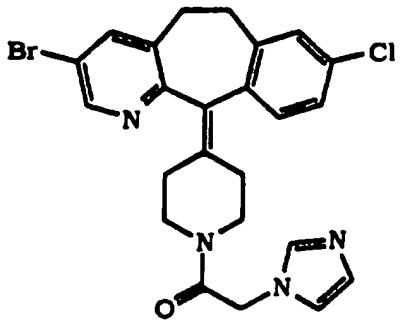
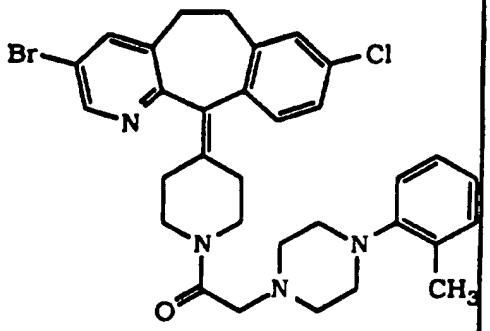
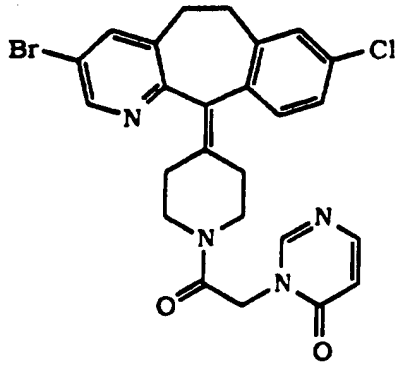
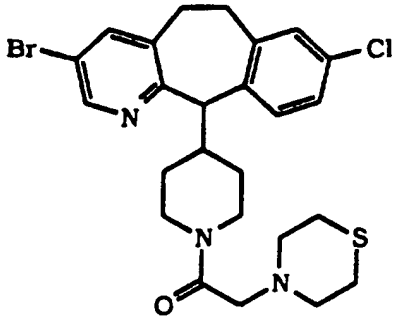


Combine 50 mg (0.11 mmol) of the compound of Example 400-N, and 1.5 mL of $SOCl_2$ and stir a room temperature overnight. Concentrate *in vacuo* to a residue, add 2.0 mL of DMF to the residue, then add 20 mg (0.2 mmol) of 1,2,4-triazole sodium salt and heat to 100°C overnight. Cool the mixture, concentrate *in vacuo* to remove most of the solvent, wash with water (3 times), then dry the resiude over Na_2SO_4. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 75% (10%NH_4OH in MeOH) in CH_2Cl_2) to give 26 mg of the product compound. Mass Spec.: MH^+ = 498

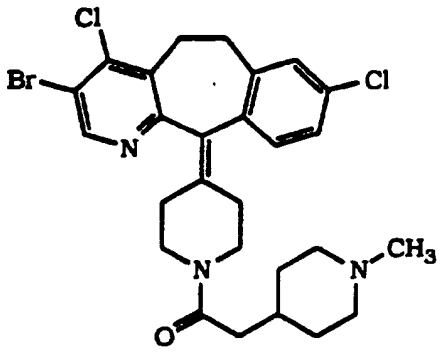
Using the appropriate starting compound and substantially the same procedure as described for Example 412, but substituting the amine nucleophile indicated in place of the 1,2,4-triazole sodium salt, the compounds in Table 5 were prepared:

TABLE 5

Amine Nucleophile	Product Compound	Analytical Data
piperidine (solvent is CH_2Cl_2 instead of DMF)	 Example 412-A	Mass Spec.: MH^+ = 514.2
thiomorpholine (solvent is CH_2Cl_2 instead of DMF)	 Example 412-B	Mass Spec.: MH^+ = 532.1
piperazine (solvent is CH_2Cl_2 instead of DMF)	 Example 412-C	Mass Spec.: MH^+ = 515
morpholine (solvent is CH_2Cl_2 instead of DMF)	 Example 412-D	Mass Spec.: MH^+ = 516.1

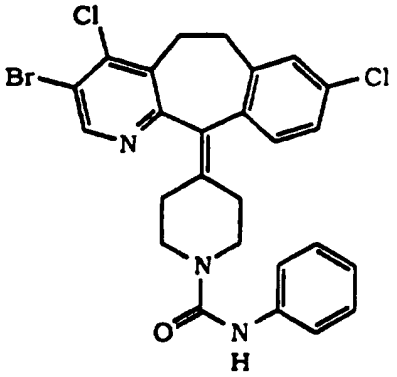
imidazole (solvent is CH_2Cl_2 instead of DMF)	 Example 412-E	Mass Spec.: MH^+ = 497.2
N-(2-methyl-phenyl)-piperazine (solvent is CH_2Cl_2 instead of DMF)	 Example 412-F	Mass Spec.: MH^+ = 605.
4(3H)-pyrimidone	 Example 412-G	Mass Spec.: MH^+ = 525.1
thiomorpholine	 Example 412-H	m.p. = 105°-105.6°C Mass Spec.: MH^+ = 536

EXAMPLE 413



Combine 0.32 g of the product from Preparative Example 46, of WO 95/10516 and 2 mL of anhydrous CH_2Cl_2 and add 6 mL of a mixture of 4.17 g of N-methyl-4-piperidylacetic acid, 1.03 mL of methanesulfonyl chloride, 6.83 mL of Et_3N and 50 mL of CH_2Cl_2. Stir at 25°C overnight, then add 1 N NaOH (aqueous) and shake well. Separate the layers, dry the organic phase over $MgSO_4$, and concentrate to a residue. Chromatograph the residue (silica gel, 3% MeOH/CH_2Cl_2 + NH_4OH) to give 0.19 g (45% yield) of the product compound. m.p.= 105°C (dec); Mass Spec.: MH^+ = 564.

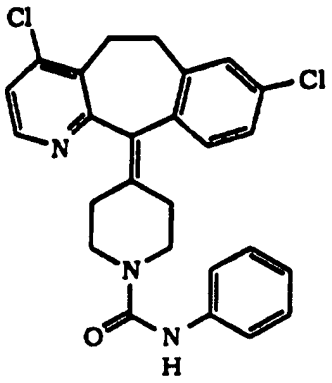
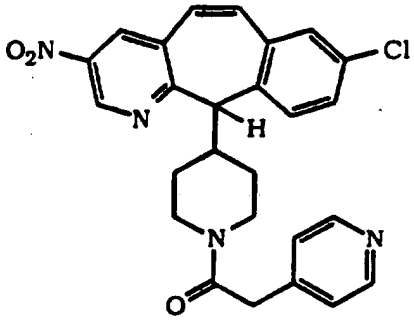
EXAMPLE 414



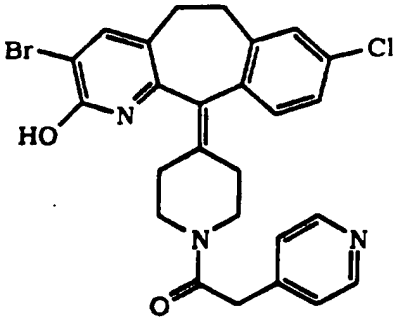
Combine 84 mg of the product from Preparative Example 46, of WO 95/10516, 5 mL of pyridine and 0.04 mL of phenylisocyanate and stir at 25°C for 48 hours. Concentrate *in vacuo* to a residue, dilute with CH_2Cl_2 and wash with saturated $NaHCO_3$ (aqueous). Dry over $MgSO_4$, concentrate to a residue and chromatograph (silica gel, 50-70% hexane/EtOAc) to give 14 mg (13% yield) of the product compound. m.p. = 125.6°C (dec); Mass Spec.: MH^+ = 544

Using the starting compound indicated, the compounds in Table 6 were prepared via substantially the same procedure as described for Example 414:

TABLE 6

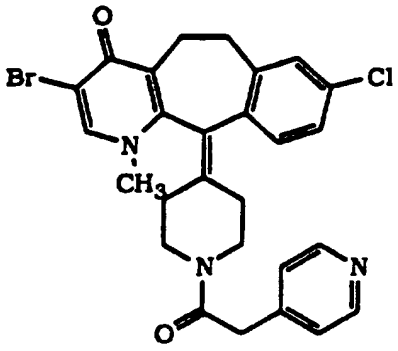
Starting Compound	Product Compound	Analytical Data
Preparative Example 28 of WO 95/10516	 Example 414-A	m.p. = 131.8°C (dec.) Mass Spec.: MH^+ = 464
Preparative Example 53A	 Example 414-B	Mass Spec.: MH^+ = 475.2

EXAMPLE 415



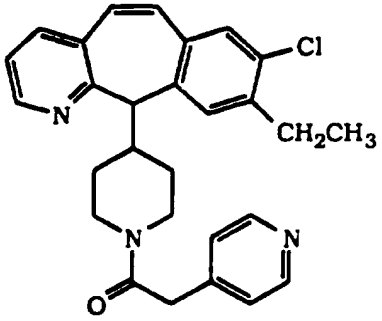
Combine 0.64 g of the product from Example 411-C and 16 mL of glacial HOAc, and add 15 mL of a 0.54 M solution of bromine in HOAc at 25°C under N_2. After 10 minutes, pour the mixture into water, filter to collect the resulting solid, and wash with water. Dry the solid under vacuum, then chromatograph (silica gel, 6-15% MeOH/CH_2Cl_2) to give 0.26 grams (35% yield) of the product compound. m.p. = 150.0 °C (dec), Mass Spec.: MH^+ = 526

EXAMPLE 416



Combine 0.33 g of the product from Preparative Example 57, 2 mL of anhydrous CH_2Cl_2, and 10 mL of a mixture of 7.20 g of 4-pyridylacetic acid hydrochloride, 1.61 mL of methanesulfonylchloride, 27 mL of Et_3N and 60 mL of $CH2Cl_2$, and stir at 25 °C for 48 hours. Dilute the mixture with CH_2Cl_2, wash with saturated $NaHCO_3$ (aqueous), then with brine. Dry over $MgSO_4$, concentrate to a residue and chromatograph (silica gel, 5% MeOH/CH_2Cl_2 + NH_4OH) to give 0.23 g (55% yield) of the product compound. m.p. = 142 °C (dec); Mass Spec.: MH^+ = 540

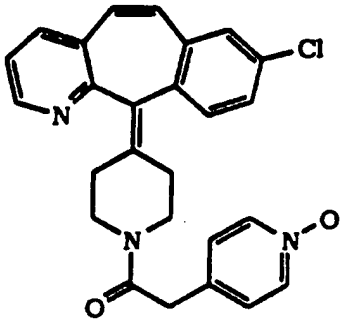
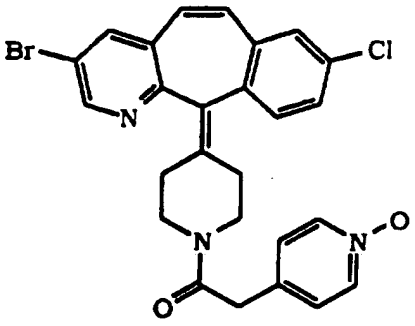
EXAMPLE 417



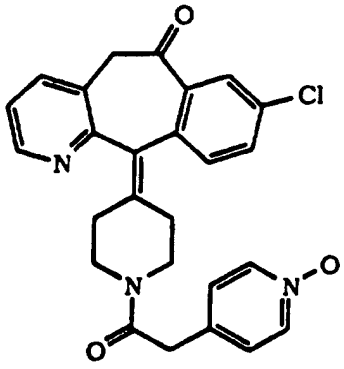
React the product from Preparative Example 35, of WO 95/10516, with 4-pyridylacetic acid via substantially the same procedure as described for Example 266, of WO 95/10516, to give the product compound. Mass Spec.: MH^+ = 458

Using the appropriate carboxylic acid and the starting compound indicated, the compounds in Table 7 were prepared via substantially the same procedure as described for Example 417:

TABLE 7

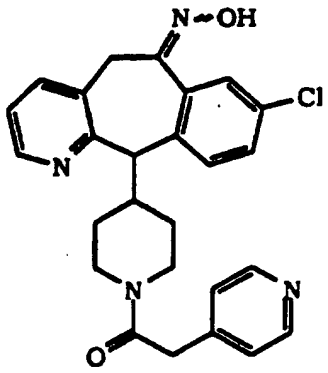
Starting Compound	Product Compound	Analytical Data
Preparative Example 37B of WO 95/10516	 Example 417-A	Mass Spec.: MH^+ = 444
Preparative Example 58	 Example 417-B	Mass Spec.: MH^+ = 522

EXAMPLE 418



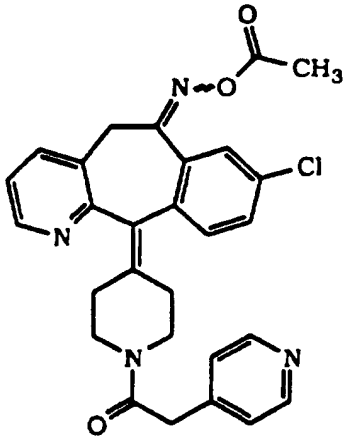
Following the procedure of Example 283, of WO 95/10516, except using 4-pyridylacetic acid N-oxide gave the product compound. Mass Spec.: MH^+ = 460

EXAMPLE 419



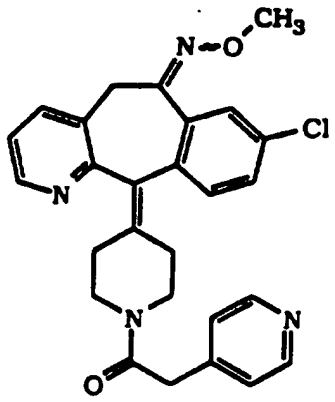
Dissolve 4.01 g (8.42 mmol) of the compound of Example 410-L in EtOAc and add 14.25 g (63.1 mmol) of finely powdered $SnCl_2$ dihydrate and stir the mixture for 5 hours. Add 150 mL of saturated NaF (aqueous) and stir for 15 min, then separate the layers and dry the organic phase over $MgSO_4$. Filtration and concentrate *in vacuo* to a residue, then chromatograph (silica gel, 95% CH_2Cl_2/MeOH + NH_4OH) to give 2.95 g of the product compound. Mass Spec.: MH^+ = 461

EXAMPLE 420



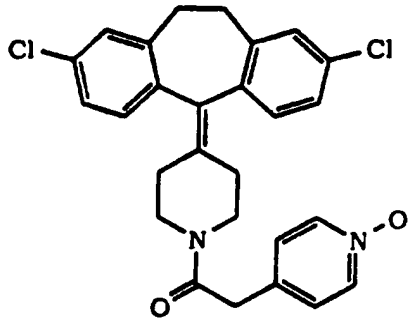
Combine 0.50 g (1.08 mmol) of the compound of Example 419 and 10 mL of anhydrous CH_2Cl_2, and add 0.11 mL (1.62 mmol) of CH_3COCl. Add 0.34 mL (4.32 mmol) of pyridine and stir at room temperature for 2.5 hours. Dilute the mixture with saturated $NaHCO_3$ (aqueous), extract with CH_2Cl_2, wash the extracts with brine and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 10% MeOH/CH_2Cl_2 + NH_4OH) to give 0.271 g of the product compound. Mass Spec.: MH^+ = 503

EXAMPLE 421



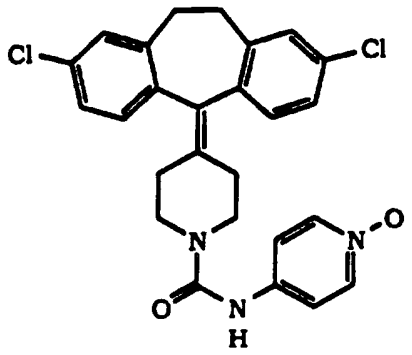
Combine 0.65 g (1.41 mmol) of the product compound of Example 419, 20 mL of CH_2Cl_2, 0.22 mL (3.52 mmol) of methyl iodide, 4.4 mL of 10% NaOH (aqueous) and 68 mg (0.21 mmol) of tetra-*n*--butyl-ammonium bromide. Stir the mixture for 5 hours, then separate the layers and dry the organic phase over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 5% MeOH/CH_2Cl_2 + NH_4OH) to give 169 mg of the product compound. Mass Spec.: MH^+ = 475

EXAMPLE 422



Combine 0.1 g (0.21 mmol) of the product compound of Example 411-L and 10 mL of CH_2Cl_2, add 0.11 g (0.66 mmol) of MCPBA and stir at ambient temperature for 1 hour. Wash with saturated $NaHCO_3$ (aqueous), dry over $MgSO_4$, and concentrate *in vacuo* to give 0.14 gm of the product compound. m.p.=100°-104°C

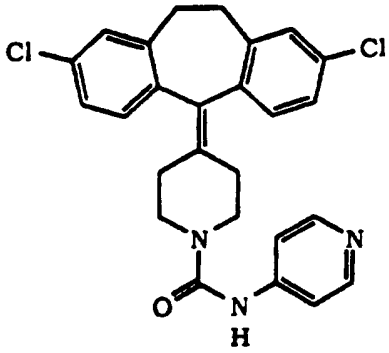
Using the compound of Example 423 and following substantially the same procedure as described for Example 422 the compound:



(Example 422-A)

was prepared. Mass Spec.: (FAB) MH^+ = 480.2

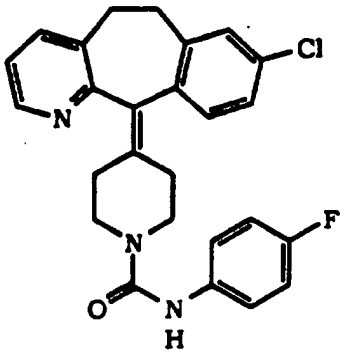
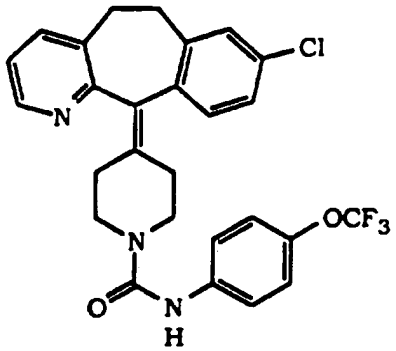
EXAMPLE 423



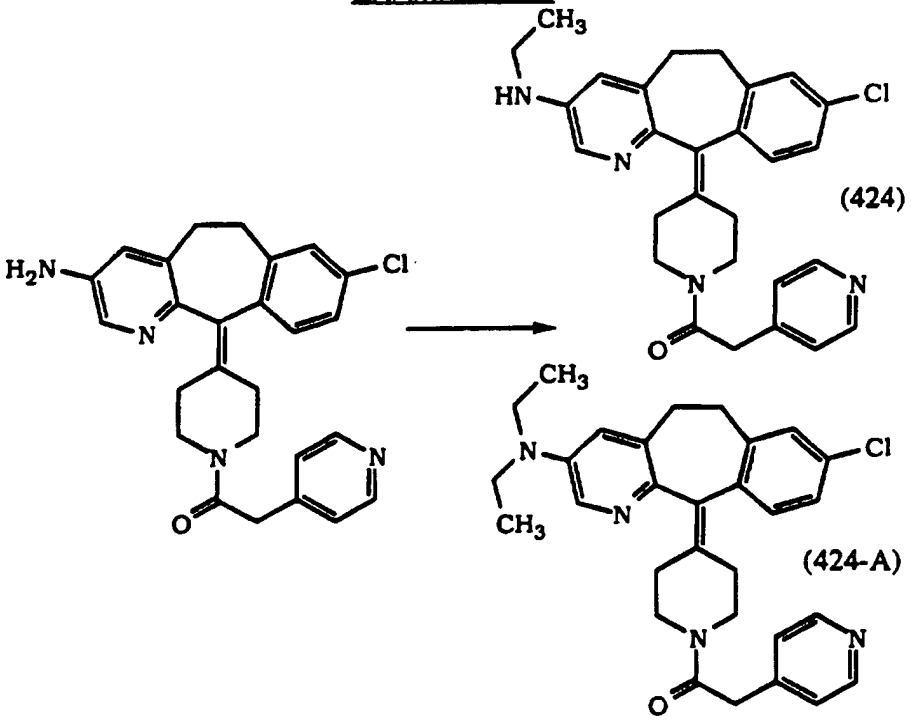
Combine 0.4 g (1.22 mmol) of the product compound of Preparative Example 59 and 0.2 g (1.2 mmol) of 4-aminopyridylethylcarbamate and heat to 180°C under a dry N_2 atmosphere for 2 hours. Cool the mixture and crystallize the product by adding EtOAc to give 0.49 g of the product compound. m.p.= 206.4°-207°C; Mass Spec.: (FAB) MH^+=464.0

Using the appropriate ethylcarbamate and the starting compound indicated, the compounds in Table 8 were prepared via substantially the same procedure as described for Example 423:

TABLE 8

Starting Compound	Product Compound	Analytical Data
Preparative Example 1, Step G of WO 95/10516	 Example 423-A	-----
Preparative Example 1, Step G of WO 95/10516	 Example 423-B	-----

EXAMPLE 424

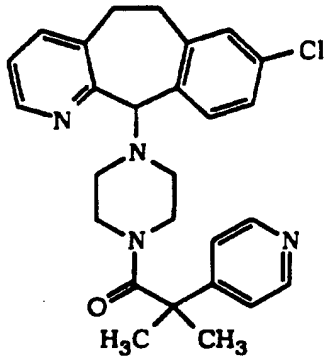


(424)

(424-A)

Combine 1 g of the product of Example 402 and 20 mL of MeOH, cool to ~0°C, and adjust to pH = 3 by adding 1 N HCl (aqueous). Add 1.25 mL of CH_3CHO and 1.41 g of $NaCNBH_3$, and stir the mixture for 1 hour. Concentrate *in vacuo* to a residue, extract with 100 mL of CH_2Cl_2 and wash the extract with 100 mL of 10% $NaHCO_3$, then with 100 mL of water. Dry over $MgSO_4$, concentrate *in vacuo* to a residue and chromatograph (silica gel, 1.5% (10% NH_4OH in MeOH)/CH_2Cl_2) to give 0.158 g of the product compound of Example 424 and 0.198 g of the product compound Example 424-A. Mass Spec. (424): MH^+ = 474. Mass Spec. (424-A): MH^+ = 502.

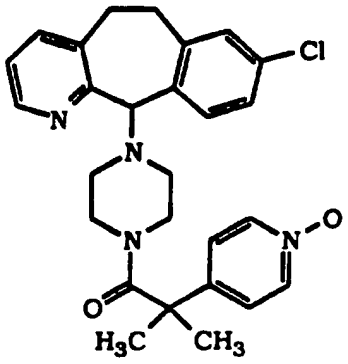
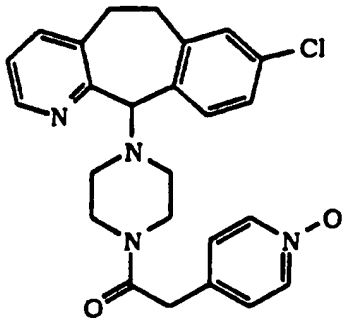
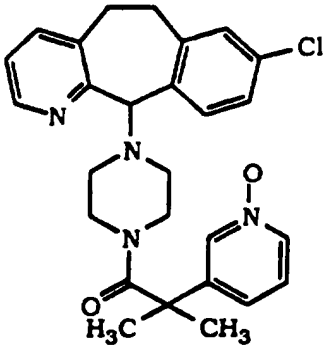
EXAMPLE 425

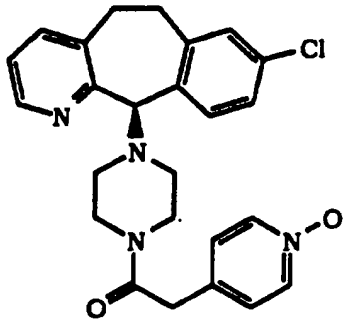
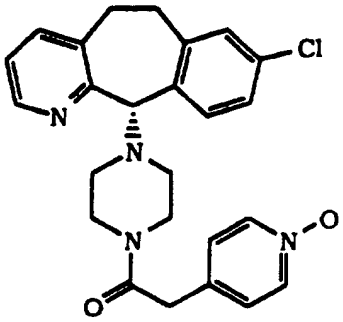
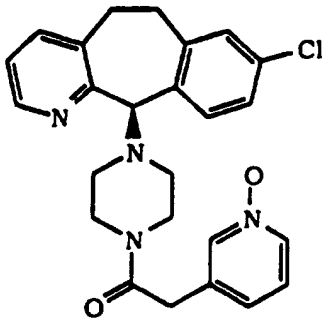
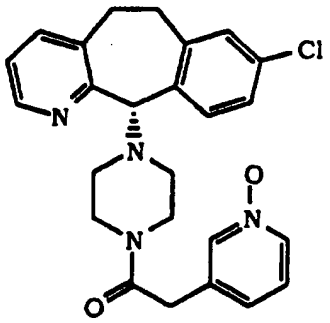


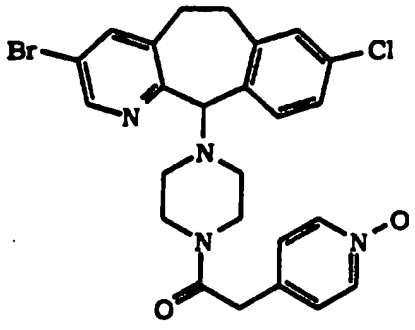
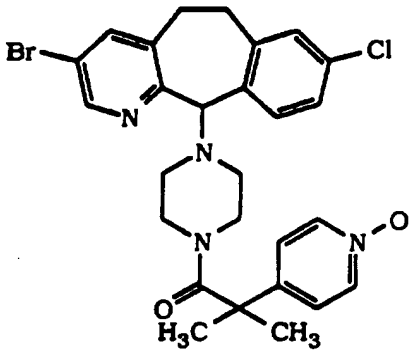
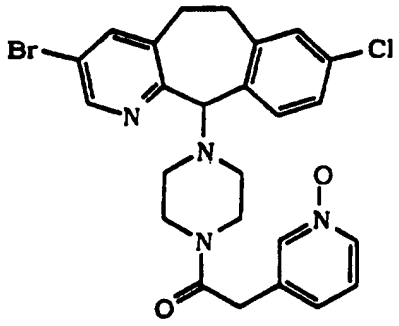
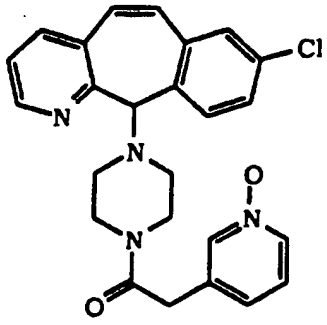
React the products of Preparative Example 7, Step C, of WO 95/10516, and Preparative Example 26, of WO 95/10516, via substantially the same procedure as described for Example 75, of WO 95/10516, to give the title compound. Mass Spec.: MH^+ = 461.35

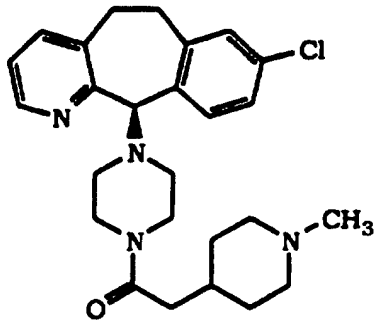
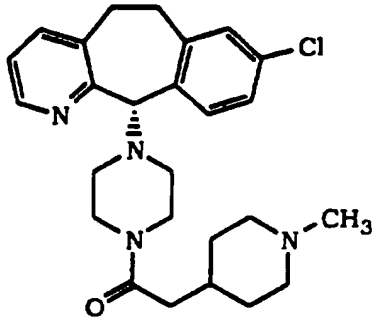
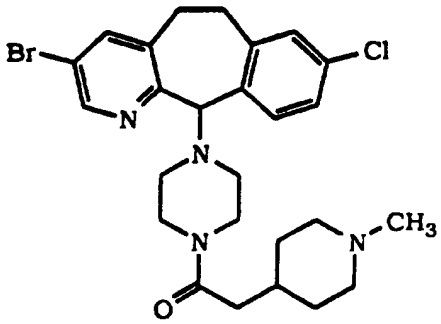
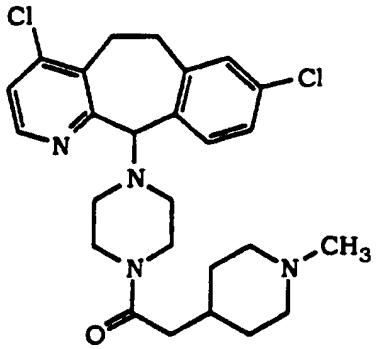
Using the appropriate carboxylic acid and the starting compound indicated, the compounds in Table 9 were prepared via substantially the same procedure as described for Example 425:

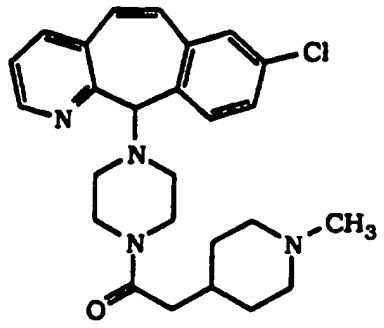
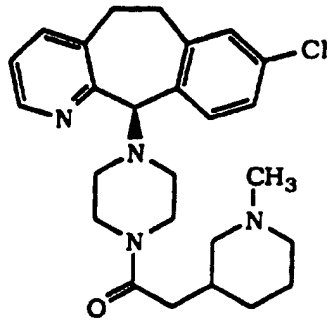
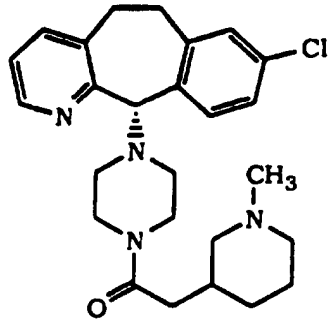
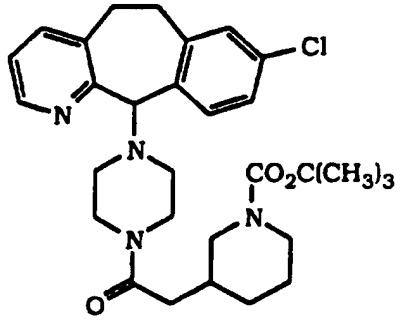
TABLE 9

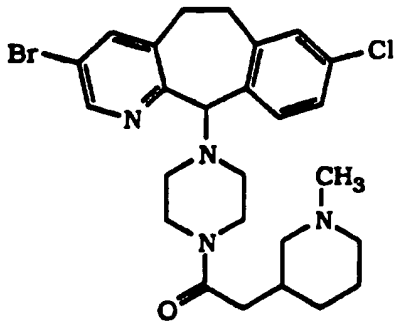
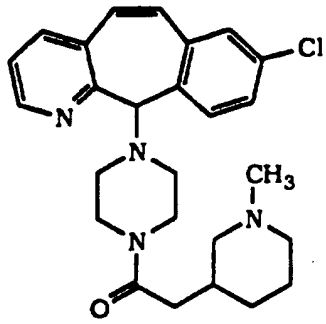
Starting Compound	Product Compound	Analytical Data
Preparative Example 7 of WO 95/10516	 Example 425-A	Mass Spec.: MH^+ = 477.2
Preparative Example 7 of WO 95/10516	 Example 425-B	Mass Spec.: MH^+ = 449.3
Preparative Example 7 of WO 95/10516	 Example 425-C	Mass Spec.: MH^+ = 477.2

Preparative Example 19 of WO 95/10516 R(+)-isomer	 Example 425-D	Mass Spec.: MH^+ = 449.2
Preparative Example 19 of WO 95/10516 S(-)-isomer	 Example 425-E	Mass Spec.: MH^+ = 449.2
Preparative Example 19 of WO 95/10516 R(+)-isomer	 Example 425-F	Mass Spec.: MH^+ = 449.3
Preparative Example 19 of WO 95/10516 S(-)-isomer	 Example 425-G	Mass Spec.: MH^+ = 449.3

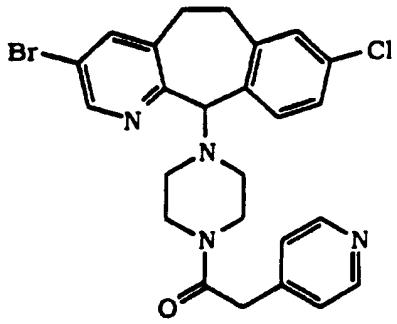
Preparative Example 40 of WO 95/10516	 Example 425-H	Mass Spec.: MH^+ = 527.0
Preparative Example 40 of WO 95/10516	 Example 425-J	Mass Spec. MH^+ = 555.3
Preparative Example 40 of WO 95/10516	 Example 425-K	Mass Spec.: MH^+ = 527.1
Preparative Example 38 of WO 95/10516	 Example 425-L	Mass Spec.: MH^+ = 447.2

Preparative Example 19 of WO 95/10516 R(+)-isomer	 Example 425-M	Mass Spec.: MH^+ = 453
Preparative Example 19 of WO 95/10516 S(-)-isomer	 Example 425-N	Mass Spec.: MH^+ = 453
Preparative Example 40 of WO 95/10516	 Example 425-O	Mass Spec.: MH^+ = 531.25
Preparative Example 41 of WO 95/10516	 Example 425-P	Mass Spec.: MH^+ = 487.35

Preparative Example 38 of WO 95/10516	 Example 425-Q	Mass Spec.: MH^+ = 451.35
Preparative Example 19 of WO 95/10516 R(+)-isomer	 Example 425-R	Mass Spec.: MH^+ = 453.35
Preparative Example 19 of WO 95/10516 S(-)-isomer	 Example 425-S	Mass Spec.: MH^+ = 453.35
Preparative Example 7 Step C of WO 95/10516	 Example 425-T	Mass Spec.: MH^+ = 539.45

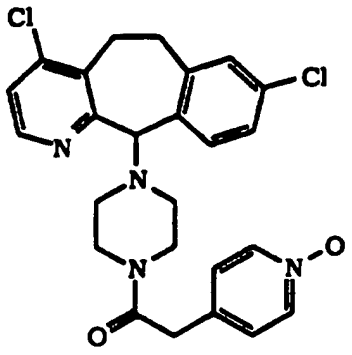
Preparative Example 40 of WO 95/10516	 Example 425-U	Mass Spec.: MH^+ = 531.35
Preparative Example 38 of WO 95/10516	 Example 425-V	Mass Spec.: MH^+ = 451.4

EXAMPLE 426



React the product of Preparative Example 40, of WO 95/10516, and 3-pyridylacetic acid via substantially the same procedure as described for Example 351, of WO 95/10516, to give the title compound. Mass Spec.: MH^+ = 511

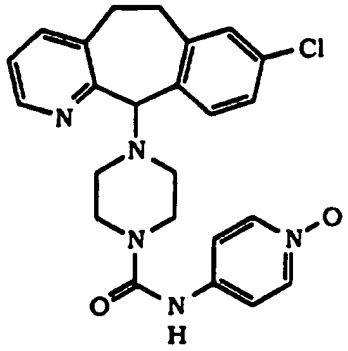
Using the appropriate carboxylic acid and the compound of Preparative Example 41 of WO 95/10516, and following substantially the same procedure as described for Example 426, the compound:



(Example 426-A)

was prepared. Mass Spec.: MH^+ = 483.2

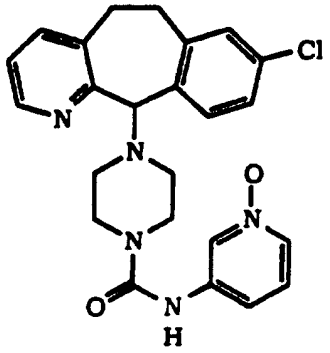
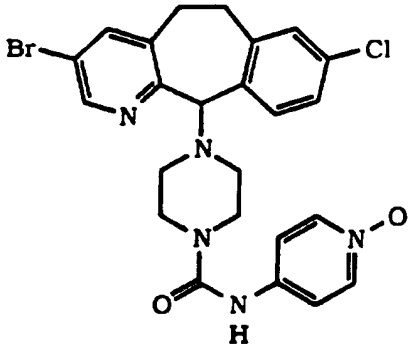
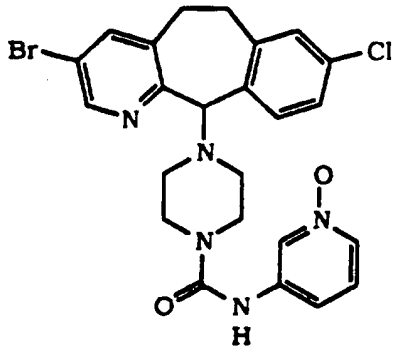
EXAMPLE 427



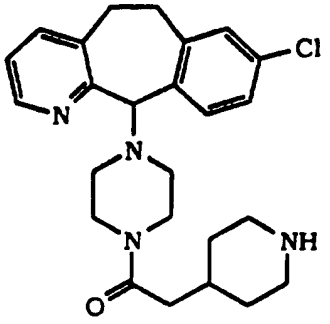
Combine 0.288 g (1.76 mmol) of the product of Preparative Example 63 and 25 mL of anhydrous toluene, heated at (110°C) for 0.5 hours, then cool to 25°C. Add a solution of 0.1 g (0.293 mmol) of the product of Preparative Example 7, Step C, of WO 95/10516, in 1.5 mL of anhydrous toluene, and stir at 25°C under an argon atmosphere for 112 hours. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 3%-4% (10% NH_4OH in MeOH)/CH_2Cl_2) to give 0.065 g of the title compound. Mass Spec.: MH^+ = 450.3

Using the appropriate azide and the starting compound indicated, the compounds in Table 10 were prepared via substantially the same procedure as described for Example 427:

TABLE 10

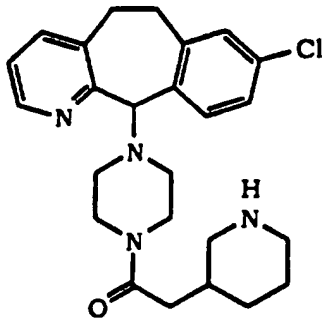
Starting Compound	Product Compound	Analytical Data
Preparative Example 7, Step C of WO 95/10516	 Example 427-A	Mass Spec.: MH^+ = 450.1
Preparative Example 40 of WO 95/10516	 Example 427-B	Mass Spec.: MH^+ = 528.1
Preparative Example 40 of WO 95/10516	 Example 427-C	Mass Spec.: MH^+ = 528.1

EXAMPLE 428



Combine 14.73 g (27.3 mmol) of the compound from Example 193, of WO 95/10516, and 125 mL of anhydrous MeOH, and add (in portions) 300 mL of a 10% solution of concentrated H_2SO_4 in dioxane. Stir the mixture at 25°C for 2 hours, then pour into water and adjust to pH =13 with 50% NaOH (aqueous). Extract with CH_2Cl_2, wash the extract with water and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 10% (10% NH_4OH in MeOH)/CH_2Cl_2) to give 8.9 g of the title compound. Mass Spec.: MH^+ = 539

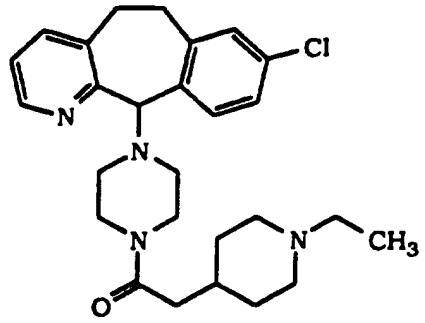
Using the compound of Example 425-T, and following substantially the same procedure as described for Example 428, the compound:



(Example 428-A)

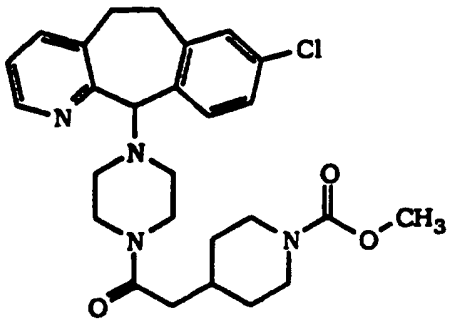
was prepared. Mass Spec.: MH^+ = 439.45

EXAMPLE 429



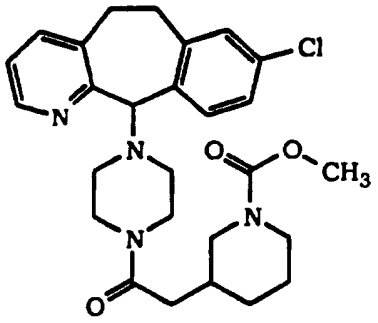
Combine 0.5 g (1.14 mmol) of the compound of Example 428 and 10 mL of 0.6 N HCl in CH_2Cl_2, stir for 10 minutes and concentrate *n vacuo* to a residue. Add 20 mL of anhydrous MeOH, then add 0.2006 g (4.56 mmol) of CH_3CHO, 0.0859 g (1.36 mmol) $NaCNBH_3$ and 0.5 g of 3A molecular sieves, and heat at 40°C for 115 hours. Filter the mixture, wash the sieves with MeOH and concentrate the combined filtrates *in vacuo* to a residue. Dissolve the residue in CH_2Cl_2 and wash with saturated $NaHCO_3$ (aqueous), then water and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 8% (10% NH_4OH in MeOH)/CH_2Cl_2) to give the title compound. Mass Spec.: MH^+ = 467.3

EXAMPLE 430



Combine 0.5 g (1.14 mmol) of the compound of Example 428 and 5 mL of anhydrous THF, add 0.1076 g (1.14 mmol) $ClCO_2CH_3$, and stir at 25°C for 1 hour. Concentrate *in vacuo* to a residue, add CH_2Cl_2 and wash with saturated $NaHCO_3$ (aqueous), then water. Dry the organic phase over $MgSO_4$, concentrate *in vacuo* to a residue and chromatograph (silica gel, 1.5% (10% NH_4OH in MeOH)/CH_2Cl_2) to give 0.4213 g of the title compound. Mass Spec.: MH^+ = 497.35

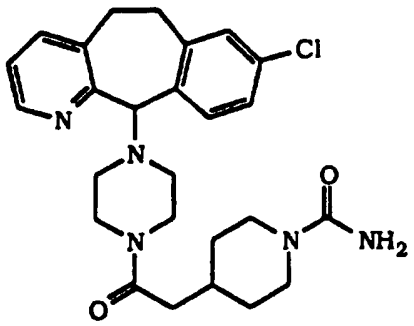
Using the compound of Example 428-A, and following substantially the same procedure as described for Example 430, the compound:



(Example 430-A)

was prepared. Mass Spec.: MH^+ = 497.35

EXAMPLE 431

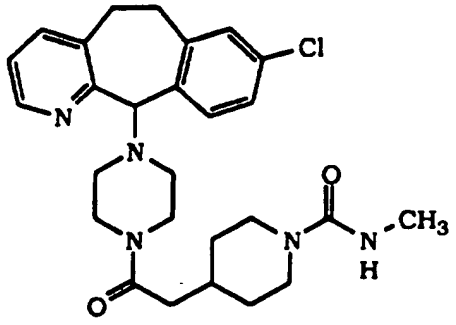
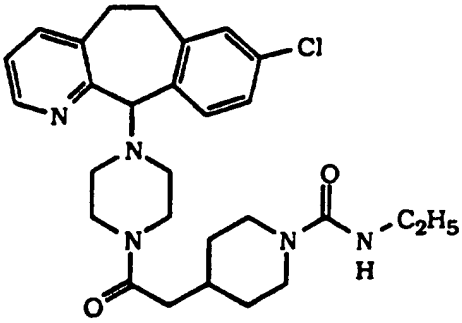
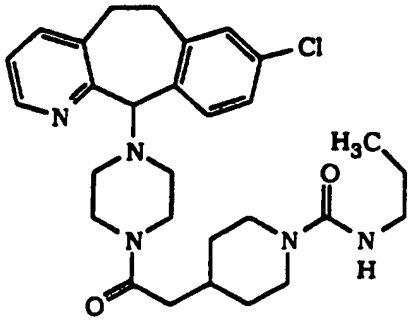


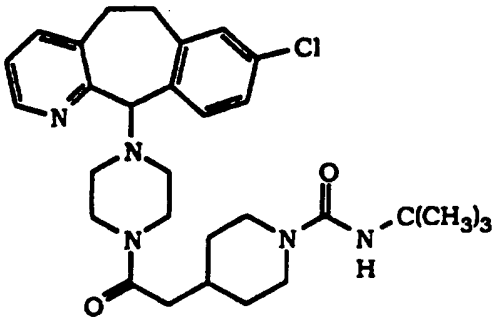
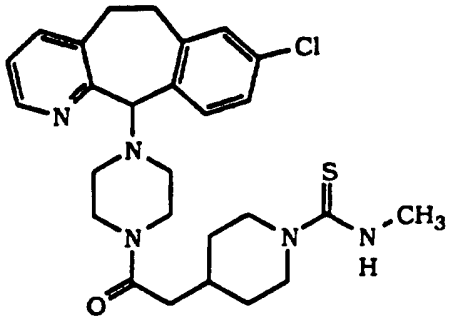
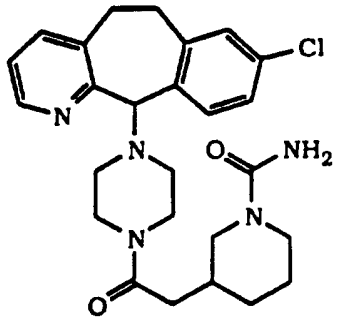
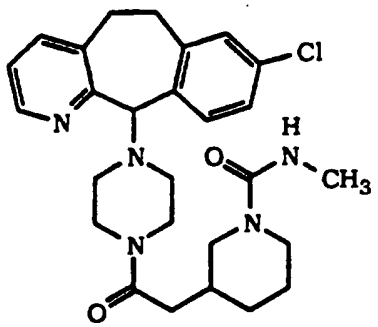
Combine 0.5 g (1.14 mmol) of the compound of Example 428 and 5 mL of anhydrous CH_2Cl_2, add 0.2624 g (2.28 mmol) of trimethylsilylisocyanate and stir under argon at 25°C for 22 hours. Add

0.1312 g (1.14 mmol) of trimethylsilylisocyanate and stir for 8 hours, then dilute with CH_2Cl_2 and wash with saturated $NaHCO_3$ (aqueous), then water. Dry over $MgSO_4$, concentrate *in vacuo* to a residue and chromatograph (silica gel, 5% (10% NH_4OH in MeOH)/CH_2Cl_2) to give 0.3878 g of the title compound. Mass Spec.: MH^+ = 482.2

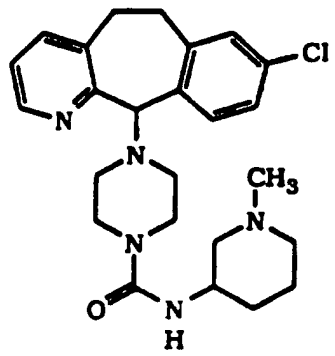
Using the isocyanate (or isothiocyanate) and starting compound indicated, the compounds in Table 11 were prepared via substantially the same procedure as described for Example 431:

TABLE 11

Starting Compound	Product Compound	Analytical Data
CH_3NCO and Example 428	 Example 431-A	Mass Spec.: MH^+ = 496.45
CH_3CH_2NCO and Example 428	 Example 431-B	Mass Spec.: MH^+ = 510.35
$CH_3(CH_2)_2NCO$ and Example 428	 Example 431-C	Mass Spec.: MH^+ = 524.35

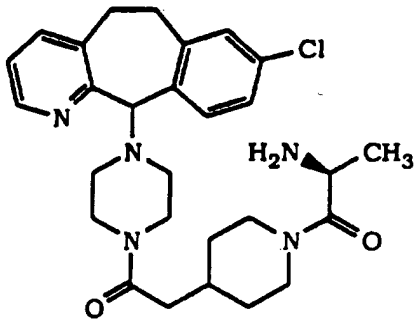
$(CH_3)_3C$-NCO and Example 428	 Example 431-D	Mass Spec.: MH^+ = 538.35
CH_3NCS and Example 428	 Example 431-E	Mass Spec.: MH^+ = 512.25
$(CH_3)_3Si$-NCO and Example 428-A	 Example 431-F	Mass Spec.: MH^+ = 482.3
CH_3NCO and Example 428-A	 Example 431-G	Mass Spec.: MH^+ = 496.35

EXAMPLE 432

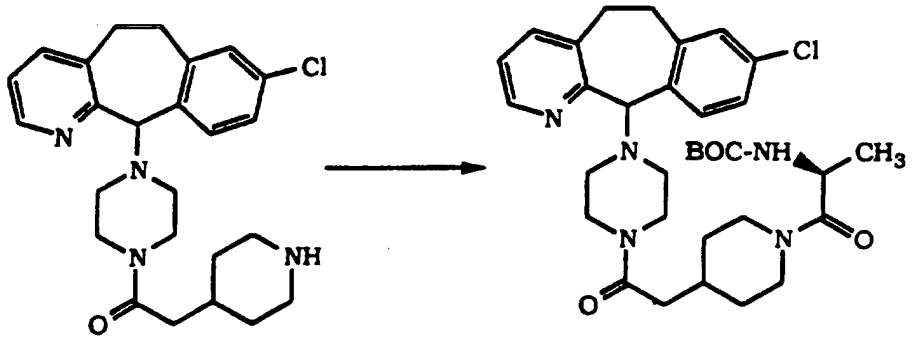


Combine 0.5 g (1.6 mmol) of the compound of Preparative Example 7, of WO 95/10516, and 1.098 g (6.4 mmol) of the compound from Preparative Example 65 and heat in a sealed vessel at 160°C for 17 hours. Cool the mixture, add CH_2Cl_2, wash with water and dry the organic phase over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 1.5% (10% NH_4OH in MeOH)/CH_2Cl_2) to give 0.0364 g of the title compound. Mass Spec.: MH^+ = 454.25

EXAMPLE 433

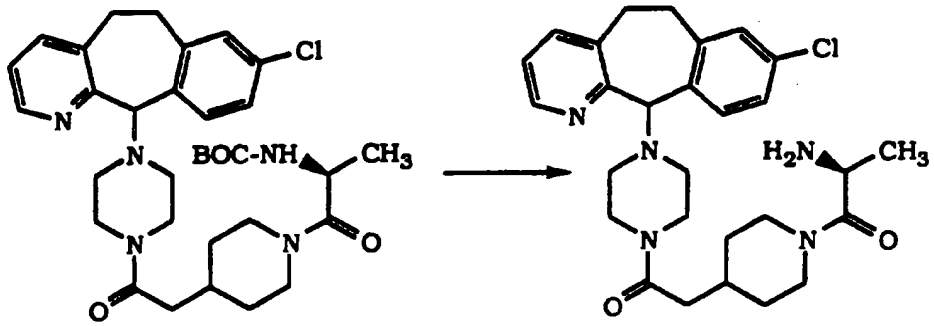


Step A:



React 0.5 g (1.59 mmol) of the compound of Example 428 and 0.3232 g (2.39 mmol) of N-(tert-butoxycarbonyl)-L-alanine (0.3232 grams) (2.39 mmoles) via essentially the same conditions as described in Example 425 to give the product compound.

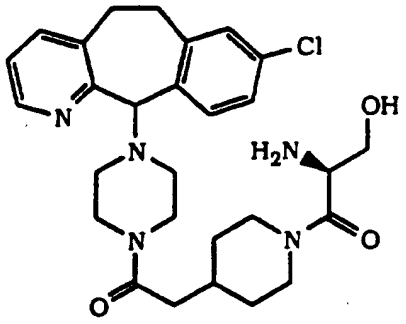
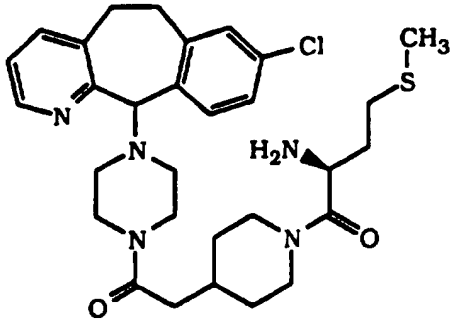
Step B:

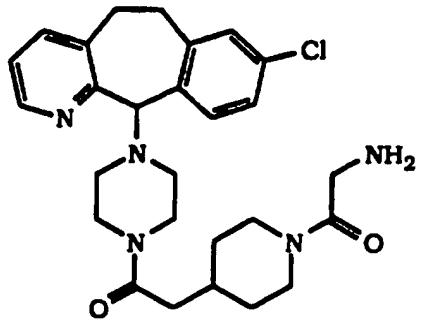


Combine the product of Step A, 5 mL of MeOH and 10 mL of 10% concentrated H_2SO_4 in dioxane and stir at 25°C for 2 hours. Neutralize with Biorad AG1X8 (OH^-) ion exchange resin, filter, wash the resin with 1:1 MeOH/water and concentrate the filtrate to a residue. Chromatograph the residue (silica gel, 8% (10% NH_4OH in MeOH)/CH_2Cl_2) to give the title compound. Mass Spec.: MH^+ = 510.35

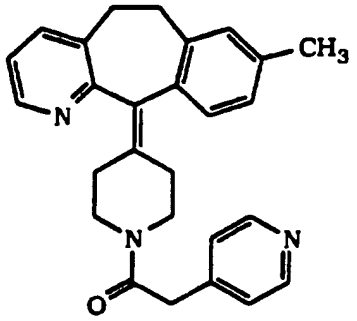
Using the appropriate BOC-amino acid and the starting compound indicated, the compounds in table 12 were prepared via substantially the same procedure as described for Example 433:

TABLE 12

Starting Compound	Product Compound	Analytical Data
BOC-L-serine and Example 428	 Example 433-A	Mass Spec.: MH^+ = 526.2
BOC-L-methionine and Example 428	 Example 433-B	Mass Spec.: MH^+ = 570.3

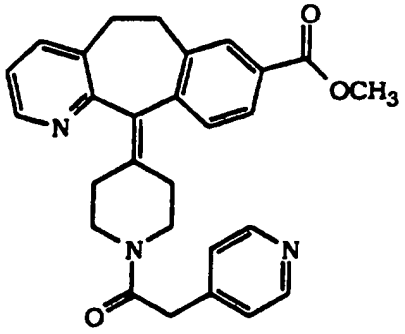
BOC-glycine and Example 428	 Example 433-C	Mass Spec.: MH^+ = 496.35

EXAMPLE 434



React the product of Preparative Example 67 with 4-pyridylacetic acid via essentially the same procedure as described for Example 411 to give the title compound. Mass Spec.: MH^+ = 410

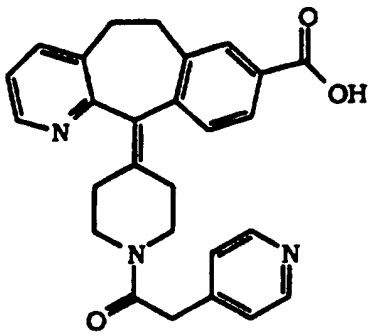
Using the appropriate carboxylic acid and the compound of Preparative Example 68, and following substantially the same procedure as described for Example 434, the compound:



(Example 434-A)

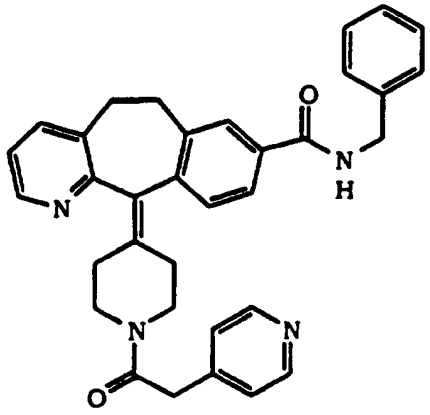
was prepared. m.p. = 68.6°-70.3°C, Mass Spec.: MH^+=454.

EXAMPLE 435



Dissolve 3.04 g (6.7 mmol) of the compound of Example 434-A in 100 mL of MeOH. Add 100 mL of a 12% KOH (aqueous) and stir for one hour at 25°C. Remove the MeOH under vacuum, neutralize to pH 7 with 12 N HCl and concentrate *in vacuo* to a residue. Dry under vacuum and triturate with 10 mL of EtOH, then filter, concentrate the filtrate *in vacuo* to give the title compound. m.p. = 238°-240° C; Mass Spec.: MH^+ = 440

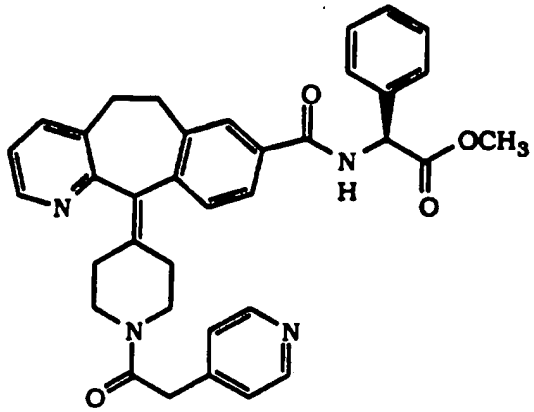
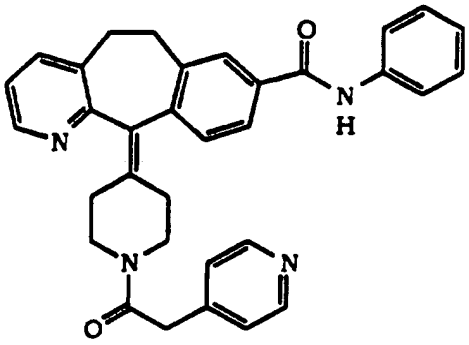
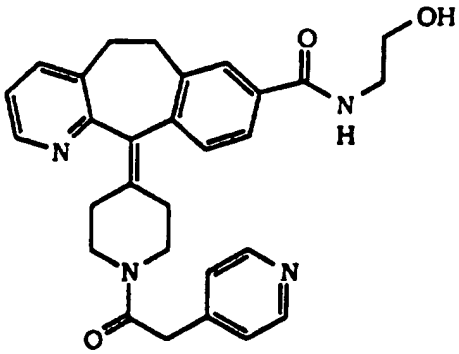
EXAMPLE 436

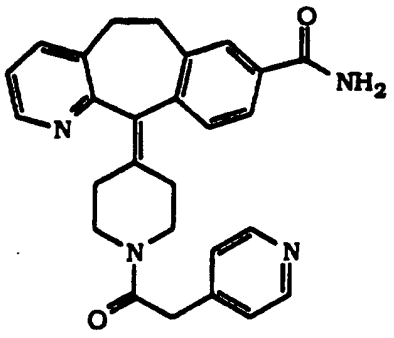


Dissolve 0.5 g (1.14 mmol) of the product of Example 435 in 25 mL of DMF, add 0.122 g (1.14 mmol) of benzylamine, 0.33 g (1.7 mmol) of DEC, 0.15 g (1.1 mmol) of HOBT, and 0.23 g (2.27 mmol) of N-methyl-morpholine, and stir at 25°C, under nitrogen for 18 hours. Concentrate *in vacuo* to a residue, add 20 mL of water and extract with 50 mL of EtOAc. Dry the organic layer over $MgSO_4$ and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 98% CH_2Cl_2/MeOH + NH_4OH) to give the product compound. m.p.=118°-120°C; Mass Spec.: MH^+=529

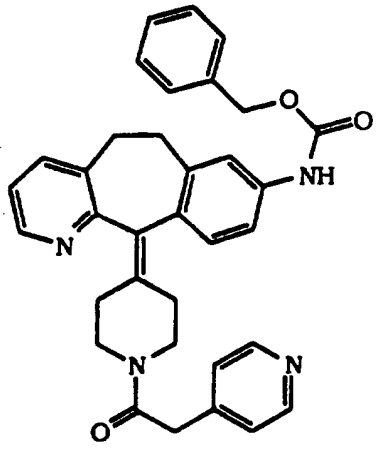
Using the appropriate amine and the starting compound indicated, the compounds in Table 13 were prepared via substantially the same procedure as described for Example 436:

TABLE 13

Starting Compound	Product Compound	Analytical Data
S-phenyl-alanine methyl ester and Example 435	 Example 436-A	m.p. = 116.9°-118.4°C Mass Spec.: MH^+ = 622
analine and Example 435	 Example 436-B	m.p. = 137.8°-139.9°C Mass Spec.: MH^+ = 516
ethanolamine and Example 435	 Example 436-C	m.p. = 130.9°-132.5°C Mass Spec.: MH^+ = 482

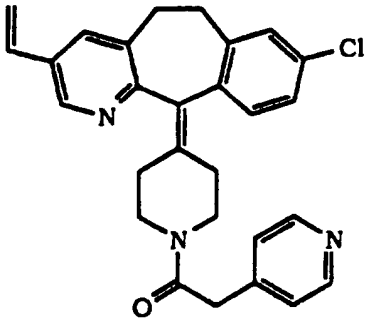
NH_4Cl and Example 435	 Example 436-D	m.p. = 133.2°-133.5°C Mass Spec.: MH^+ = 439

EXAMPLE 437



Dissolve 0.18 g (0.41 mmol) of the product of Example 435 in 2 mL of toluene, add 0.12 g (0.43 mmol) of diphenylphosphoryl azide, 0.041 g (0.41 mmol) of Et_3N, and 0.092 g (0.44 mmol) of benzyl alcohol and heat at reflux under nitrogen for 18 hours. Concentrate *in vacuo* to a residue and chromatograph (silica gel 95% CH_2Cl_2/MeOH) to obtain the title compound. m.p. = 132.8°-133.7°C; MH^+ = 545

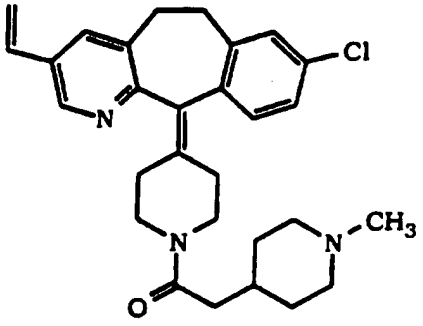
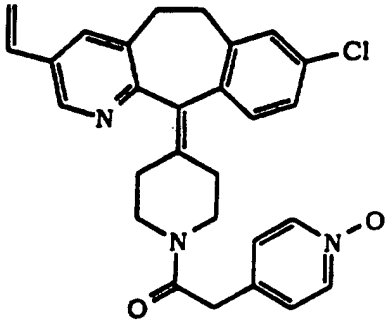
EXAMPLE 438



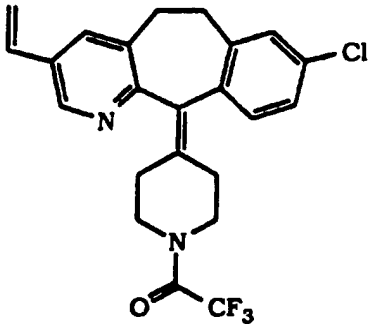
React the product of Preparative Example 70 with 4-pyridylacetic acid via essentially the same procedure as described for Example 411 to give the title compound. Mass Spec.: (FAB) $MH^+ = 456$

Using the appropriate carboxylic acid and the starting compound indicated, the compounds of Table 14 were prepared via substantially the same procedure as described for Example 438:

TABLE 14

Starting Compound	Product Compound	Analytical Data
Preparative Example 70	 Example 438-A	Mass Spec.: (FAB) MH^+ = 476
Preparative Example 70	 Example 438-B	Mass Spec.: (FAB) MH^+ = 472

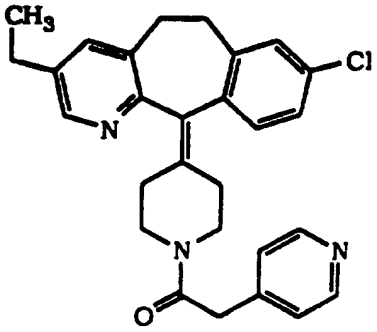
EXAMPLE 439



Combine 1.7 g (5 mmol) of the product of Preparative Example 70, Step D, and 10 mL of anhydrous pyridine at 0°C under N_2 atmosphere,

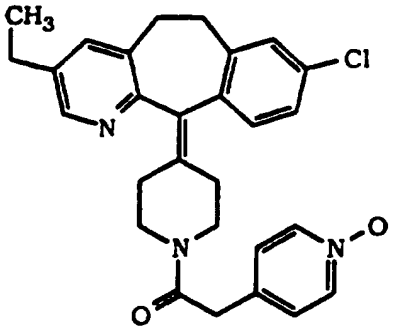
then slowly add (dropwise) 1 mL (7 mmol) of TFAA and stir at 25°C overnight, Dilute with 100 ml of cold water, extract with CH_2Cl_2 (2 x 75 mL), wash the extracts successfully with 10% $CuSO_4$ (aqueous) and brine, then dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel 30%40% EtOAc/hexane) to give 1.75 g of the title compound. Mass Spec.: (FAB) MH^+ = 433

EXAMPLE 440



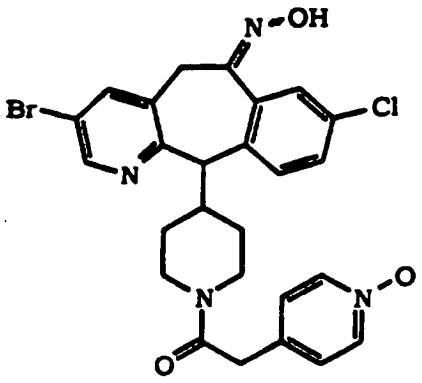
Combine 0.07 g (0.154 mmol) of the product of Example 438, 7 mL of EtOH and 12 mg of PtO_2, and hydrogenate at 25°C and atmospheric pressure for 1 hour. Filter, wash with EtOH and concentrate *in vacuo* to give 0.066 g of the title compound. Mass Spec.: (FAB) MH^+ = 458

Using the compound of Example 438-B, and following substantially the same procedure as described for Example 440, the compound:



(Example 440-A) was prepared. Mass Spec.: (FAB) MH^+ = 474

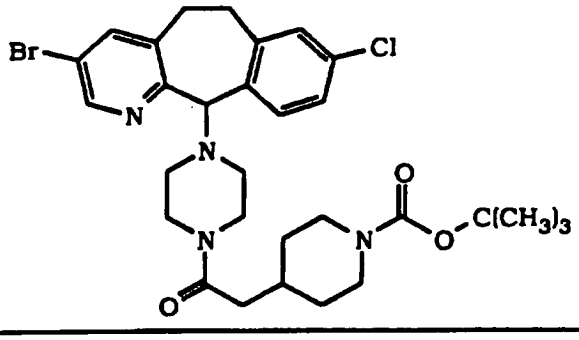
EXAMPLE 441

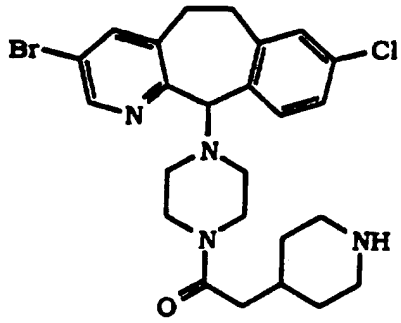
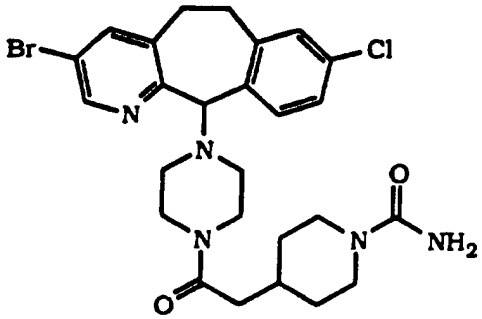
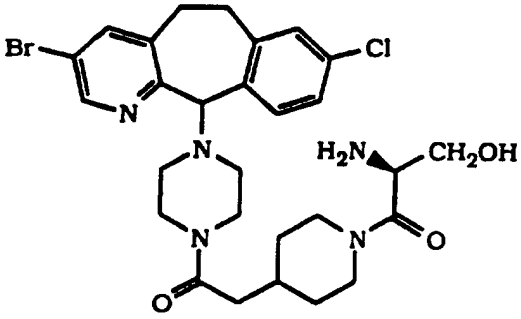
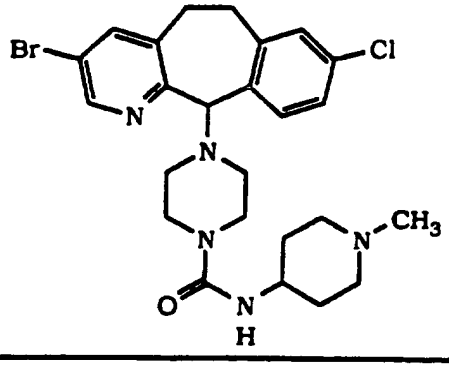


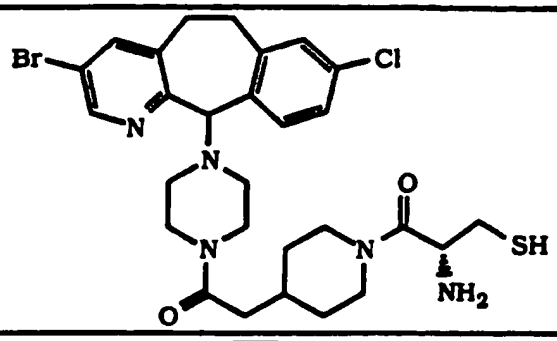
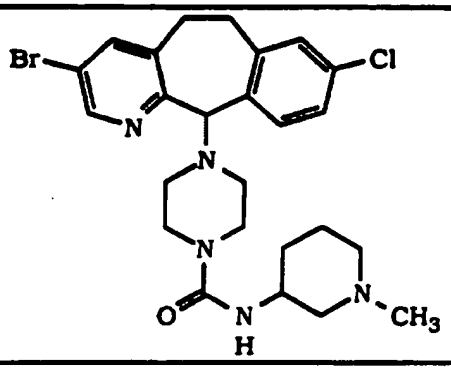
Combine 0.07 g of the compound of Example 410-R, 2 mL of THF, 0.5 mL of water, 10 drops of glacial HOAc, and 0.1 g of powdered Zn, and stir the mixture for 0.5 hours at 25°C. Purify the mixture by preparative thin layer chromatography (Prep TLC), (silica gel, 10% (10% NH_4OH in MeOH)/CH_2Cl_2), to give a total of 68 mg of the crude product. Purify again by Prep TLC), (silica gel, 13% (10% NH_4OH in MeOH)/CH_2Cl_2), to give 33 mg of the product compound. Mass Spec.: $MH^+ = 555$

The compounds in Table 15 were prepared using the product of Preparative Example 40, of WO 95/10516, and following substantially the same procedures as described for Examples 183 and 193 of WO 95/10516, and Examples 428, 431, 433-A disclosed above, as appropriate:

TABLE 15

Example No.	Compound	Analytical Data
500		Mass Spec.: $MH^+ = 619.15$

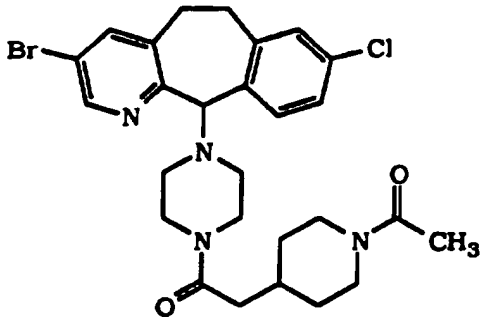
501		Mass Spec.: MH^+ = 517
502		Mass Spec.: MH^+ = 560
503		Mass Spec.: MH^+ = 604.2
504		Mass Spec.: MH^+ = 532.15

505		Mass Spec.: MH^+ = 622.1
506		Mass Spec.: MH^+ = 534.3

Analytical data for Example 505 are: H-1 NMR: δ_H (D_2O) 7.35 (1H, aromatic), 7.44 (1H, aromatic), 7.49 (1H, aromatic), 7.93 (1H, aromatic) and 8.58 (1H, aromatic).

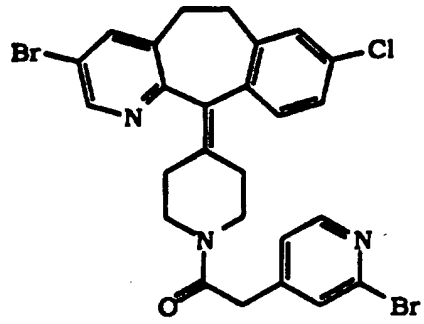
Analytical data for Example 506 are: δ_C ($CDCl_3$) (a) Tricyclic: (i) CH_2: 30.0, 30.0; (ii) CH: 146.5, 140.7, 132.0, 125.7, 130.0, 78.6; and (iii) C: 119.4, 140.3, 133.6, 135.0, 136.3, 155.4; (b) Piperazine: (i) CH_2: 43.4, 43.4, 50.8, 50.8; and (c) Piperazine N-substituent: (i) CH_3: 46.1; (ii) CH_2: 28.3, 21.4, 55.4; (iii) CH: 45.5; and (iv) C: 156.4.

EXAMPLE 507



React the compound of Example 501 with an excess of acetic anhydride in MeOH via standard procedures to form the product compound in 91% yield. Mass Spec.: MH^+ = 559

EXAMPLE 508



React the compound of Preparative Example 49 with 4-(2-bromopyridyl)acetic acid via the substantially the same procedure as described for Example 410 to give the product compound. m.p. = 134°-136.1°C; Mass Spec.: MH^+ = 588

ASSAYS

FPT IC_{50} (inhibition of farnesyl protein transferase, in vitro enzyme assay), GGPT IC_{50} (inhibition of geranylgeranyl protein transferase, in vitro enzyme assay), COS Cell IC_{50} (Cell-Based Assay) and Cell Mat Assay were determined by the methods disclosed in WO 95/10516. Results of these assays are given in Tables 16-19.

TABLE 16 - FPT INHIBITION

EXAMPLE	FPT IC_{50} (μM)	EXAMPLE	FPT IC_{50} (μM)
400 (5.210)	0.01-10	401 (5.209)	0.01-10
400-B (5.203)	0.01-10	400-C (5.200)	0.01-10
400-D (5.217)	0.01-10	400-E (5.208)	0.01-10
400-F (5.201)	0.01-10	400-G (5.204)	0.01-10
400-H (5.220)	0.01-10	400-J (5.212)	0.01-10
400-K (5.218)	0.01-10	400-L (5.206)	0.01-10
411	0.01-10	411-A	0.01-10
411-B	0.01-10	402-A	0.01-10
411-D	0.01-10	411-E	0.01-10
411-F	0.01-10	411-G	0.01-10
411-L	0.01-10	402	0.01-10
405	0.01-10	406	0.01-10
413	0.01-10	414-A	0.01-10
414	0.01-10	417	0.01-10
418	0.01-10	417-A	0.01-10
417-B	0.01-10	419	0.01-10

420	0.01-10	422	0.01-10
423	0.01-10	422-A	0.01-10
411-N	0.01-10	411-M	0.01-10
411-R	0.01-10	411-S	0.01-10
411-P	0.01-10	411-Q	10-100
411-O	0.01-10	411-X	0.01-10
411-V	0.01-10	411-T	0.01-10
411-W	0.01-10	411-U	0.01-10
425	0.01-10	425-B	0.01-10
425-A	0.01-10	425-C	0.01-10
425-E	0.01-10	425-D	0.01-10
425-G	0.01-10	425-F	0.01-10
426 (5.207)	0.01-10	425-H (5.202)	0.01-10
425-J	0.01-10	425-K	0.01-10
425-L	0.01-10	426-A	0.01-10
427	0.01-10	427-A	0.01-10
425-N	0.01-10	428	0.01-10
429	0.01-10	425-M	0.01-10
431	0.01-10	431-C	0.01-10
431-B	0.01-10	431-D	0.01-10
431-A	0.01-10	430	0.01-10
431-E	0.01-10	425-O (5.216)	0.01-10
425-P	0.01-10	425-Q	0.01-10
425-S	0.01-10	425-R	0.01-10
428-A	0.01-10	431-F	0.01-10
430-A	0.01-10	431-G	0.01-10
425-T	10-100	425-U (5.211)	0.01-10
425-V	0.01-10	434	0.01-10
434-A	0.01-10	435	0.01-10
437	10-100	411-Z	0.01-10
427-B	0.01-10	427-C	0.01-10
432	0.01-10	415	0.01-10
411-C	0.01-10	400-M	0.01-10
411-DD	0.01-10	411-EE	10-100
411-FF	0.01-10	----	----

410-W	0.01-10	410-G	0.01-10
410-H	0.01-10	410-J	0.01-10
412	0.01-10	410-L	0.01-10
403	10-100	404	0.01-10
401-A	0.01-10	400-A	0.01-10
412	0.01-10	416	0.01-10
410-M	10-100	424	0.01-10
424-A	10-100	433	0.01-10
433-A	0.01-10	433-B	0.01-10
433-C	0.01-10	436	10-100
436-A	10-100	436-B	10-100
436-C	10-100	436-D	0.01-10
410-S	10-100	410-T	0.01-10
410-U	0.01-10	410-V	0.01-10
505	0.01-10	506	0.01-10

TABLE 17

COMPARISON OF FPT INHIBITION AND GGPT INHIBITION

EXAMPLE	ENZYME INHIBITION FPT IC_{50} μM	ENZYME INHIBITION GGPT IC_{50} μM
400-D	0.01-10	>38
400-C	0.01-10	>38
400-B	0.01-10	>38
400-E	0.01-10	30%@38μM
400-F	0.01-10	0%@36μM
400-G	0.01-10	>39
400-H	0.01-10	0%@36μM
400-J	0.01-10	6%@36μM
400-K	0.01-10	0%@37μM
400	0.01-10	29%@36μM
401	0.01-10	7%@34μM
413	0.01-10	>35
417-B	0.01-10	15%@32μM
419	0.01-10	0%@41μM
411-W	0.01-10	3%@42μM
426	0.01-10	>39

425-H	0.01-10	>38
425-O	0.01-10	>38
425-U	0.01-10	>38
400-L	0.01-10	38
410-G	0.01-10	32%@33μM

TABLE 18 - ACTIVITY IN COS CELLS

Example	Inhibition of Ras Processing IC_{50} (μM)	Example	Inhibition of Ras Processing IC_{50} (μM)
411	0.01-10	411-A	0.01-10
411-B	0.01-10	411-D	0.01-10
400-D	0.01-10	400-C	0.01-10
402	10-100	411-G	0.01-10
400-G	0.01-10	400-H	0.01-10
400-K	0.01-10	411-B	0.01-10
400-D	0.01-10	400-C	0.01-10
400-G	0.01-10	413	0.01-10
417	0.01-10	418	10-100
425-E	0.01-10	426	0.01-10
425-H	0.01-10	425-J	0.01-10
425-K	0.01-10	426-A	0.01-10
425-O	0.01-10	425-P	0.01-10
425-U	0.01-10	434	0.01-10
400-L	0.01-10	410-G	0.01-10

TABLE19

INHIBITION OF TUMOR CELL GROWTH - MAT ASSAY

Example	Tumor IC_{50} (μM)	Normal IC_{50} (μM)	Example	Tumor IC_{50} (μM)	Normal IC_{50} (μM)
411-A	1.6	> 25	411	18	> 25
411-B	6.25	>25	402-A	3.1	>25
411-D	8	>25	411-E	>25	>25
400-D	4	>25	400-C	<1.6	>25
402	18	>25	400-B	<1.6	6.25
411-G	6.25 4	>25 >12.5	400-E	<1.6	18

400-F	<1.6	>25	405	12.5	>25
400-G	1.6	>25	400	1.6	>25
401	<1.6	>25	411-B	6.25	>25
402-A	3.1	>25	400-D	4	>25
400-C	<1.6	>25	400-B	<1.6	>25
400-G	1.6	>25	413	>6.25	10
417	10	18	418	25	>25
417-B	<1.6	>25	425	12.5	>25
425-B	12.5	>25	425-E	1.6	>25
426	3.1 <0.8	25 >12.5	425-H	<1.6	>25
425-J	3.1	>25	425-K	6.25	>25
426-A	6.25	>25	428	12.5	18
425-O	3.1 <0.8	6.25 6.25	425-P	>3.1	3.1
425-U	6.25	10	400-L	<1.6 <0.8	>25 >12.5

RESULTS:

1. Enzymology:

The data demonstrate that the compounds of the invention are inhibitors of Ras-CVLS farnesylation by partially purified rat brain farnesyl protein transferase (FPT). The data also show that there are compounds of the invention which can be considered as potent (IC_{50} <10 μM) inhibitors of Ras-CVLS farnesylation by partially purified rat brain FPT.

The data also demonstrate that compounds of the invention are poorer inhibitors of geranylgeranyl protein transferase (GGPT) assayed using Ras-CVLL as isoprenoid acceptor. Generally, the compounds of the invention are inactive or weakly active as geranylgeranyl transferase inhibitors at 20 μg/mL. This selectivity is important for the therapeutic potential of the compounds used in the methods of this invention, and increases the potential that the compounds will have selective growth inhibitory properties against Ras-transformed cells.

2. Cell-Based: COS Cell Assay

Western blot analysis of the Ras protein expressed in Ras-transfected COS cells following treatment with the tricyclic farnesyl protein transferase inhibitors of this invention indicated that they inhibit Ras-CVLS processing, causing accumulation of unprocessed Ras

These results provide evidence for specific inhibition of farnesyl protein transferase, but not geranylgeranyl transferase I, by compounds of this invention in intact cells and indicate their potential to block cellular transformation by activated Ras oncogenes.

3. Cell-Based: Cell Mat Assay

Tricyclic farnesyl protein transferase inhibitors of this invention also inhibited the growth of Ras-transformed tumor cells in the Mat assay without displaying cytotoxic activity against the normal monolayer.

In Vivo Anti-Tumor Studies:

Tumor cells (5 X 10^5 to 8 X 10^6) of DLD-1 (human colon carcinoma cells, ATCC # CCL 221), and PT-24 (mouse fibroblast cell line transfected with human H-ras), are innoculated subcutaneously into the flank of 5-6 week old athymic nu/nu female mice. Tumor bearing animals are selected and randomized when the tumors are established. Animals are treated with vehicle only or with a compound of the present invention in vehicle four times a day (QID) for 7 days per week for 4 weeks. The percent inhibition of tumor growth relative to vehicle controls is determined by tumor measurements. The results are reported in Table 20.

TABLE 20

IN VIVO ANTI-TUMOR STUDIES

EXAMPLE	EXPERIMENT NO.	CELL LINE	DOSE mg/kg (P.O.)	AVERAGE % TUMOR INHIBITION
400-C	1	PT-24	50	99.7
	2	PT-24	10	43.6
	3	DLD-1	50	31
	4	DLD-1	10	21
425-H	1	PT-24	50	95.1
	2	PT-24	10	68.7
	3	DLD-1	50	42
	4	DLD-1	10	37
400-F	1	PT-24	50	78.3
	2	PT-24	10	31.8
400-Q	1	DLD-1	50	70
	2	DLD-1	10	52
	3	DLD-1	50	39
	4	DLD-1	10	21

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg. to 300 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen is oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to block tumor growth. The compounds are non-toxic when administered within this dosage range.

The following are examples of pharmaceutical dosage forms which contain a compound of the invention. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

Pharmaceutical Dosage Form Examples

EXAMPLE A

Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B

Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	7	7
	Total	253	700

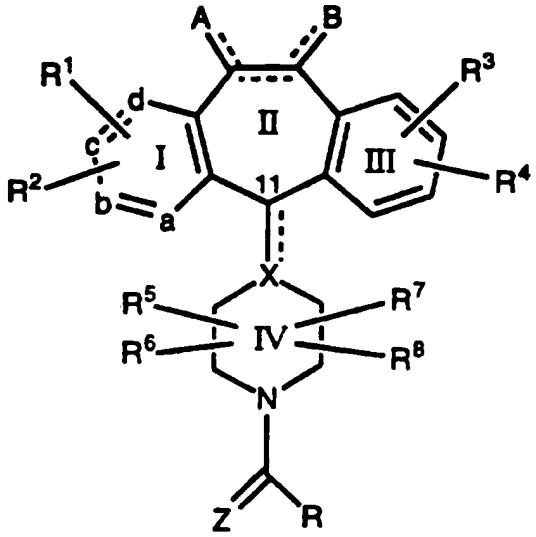
Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A method for inhibiting the abnormal growth of cells comprising administering an effective amount of a compound of Formula 1.0:



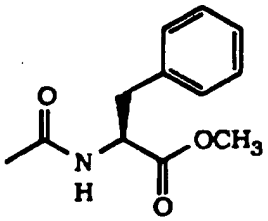
(1.0)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N or NR^9 wherein R^9 is O^-, $-CH_3$ or $-(CH_2)_nCO_2H$ wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR^1 or CR^2; or

each of a, b, c, and d are independently selected from CR^1 or CR^2;

each R^1 and each R^2 is independently selected from H, halo, $-CF_3$, $-OR^{10}$, $-COR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$ (wherein t is 0, 1 or 2), -SCN, $-N(R^{10})_2$, $-NR^{10}R^{11}$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, -CN, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-CONHR^{10}$, $-CONHCH_2CH_2OH$, $-NR^{10}COOR^{11}$, $-SR^{11}C(O)OR^{11}$,



$-SR^{11}N(R^{75})_2$ (wherein each R^{75} is independently selected from H and $-C(O)OR^{11}$), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, $-OR^{10}$ or $-CO_2R^{10}$;

R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2, or R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring;

R^5, R^6, R^7 and R^8 each independently represents H, $-CF_3$, $-COR^{10}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-OR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$, $-NR^{10}COOR^{11}$, $-N(R^{10})_2$, $-NO_2$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{11}$, $-CO_2R^{10}$, OPO_3R^{10} or one of R^5, R^6, R^7 and R^8 can be taken in combination with R^{40} as defined below to represent $-(CH_2)_r-$ wherein r is 1 to 4 which can be substituted with lower alkyl, lower alkoxy, $-CF_3$ or aryl, or R^5 is combined with R^6 to represent =O or =S and/or R^7 is combined with R^8 to represent =O or =S;

R^{10} represents H, alkyl, aryl, or aralkyl;

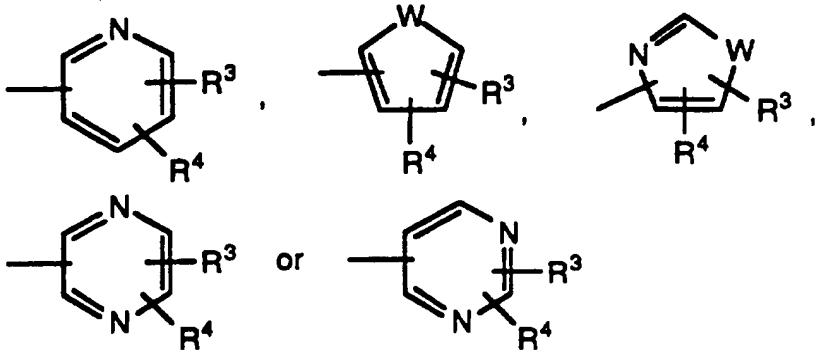
R^{11} represents alkyl or aryl;

X represents N, CH or C, which C may contain an optional double bond, represented by the dotted line, to carbon atom 11;

the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent $-NO_2$, $-R^{10}$, halo, $-OR^{11}$, $-OCO_2R^{11}$ or $-OC(O)R^{10}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2, $-(OR^{11})_2$, H and halo, dihalo, alkyl and H, $(alkyl)_2$, -H and $-OC(O)R^{10}$, H and $-OR^{10}$, =O, aryl and H, $=NOR^{10}$ or $-O-(CH_2)_p-O-$ wherein p is 2, 3 or 4;

R represents R^{40}, R^{42}, R^{44}, or R^{54}, as defined below;

R^{40} represents H, aryl, alkyl, cycloalkyl, alkenyl, alkynyl or -D wherein -D represents

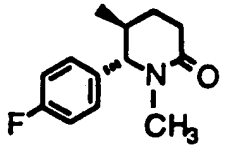
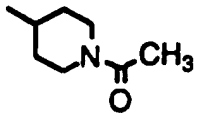
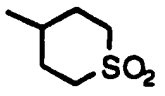
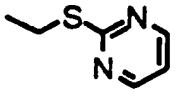
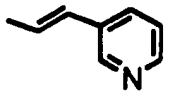
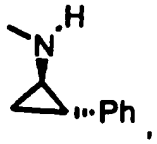
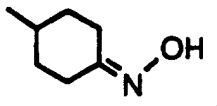
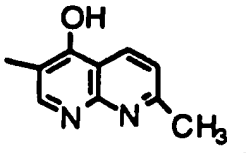
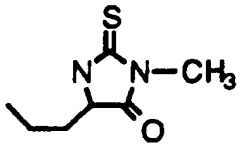
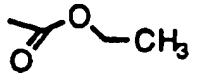
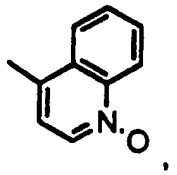
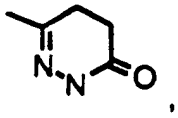
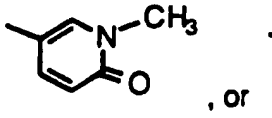
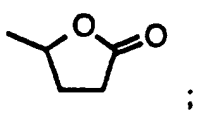


wherein R^3 and R^4 are as previously defined and W is O, S or NR^{10} wherein R^{10} is as defined above; said R^{40} cycloalkyl, alkenyl and alkynyl groups being optionally substituted with from 1-3 groups selected from halo, $-CON(R^{10})_2$, aryl, $-CO_2R^{10}$, $-OR^{12}$, $-SR^{12}$, $-N(R^{10})_2$,

$-N(R^{10})CO_2R^{11}$, $-COR^{12}$, $-NO_2$ or D, wherein -D, R^{10} and R^{11} are as defined above and R^{12} represents R^{10}, $-(CH_2)_mOR^{10}$ or $-(CH_2)_qCO_2R^{10}$ wherein R^{10} is as previously defined, m is 1 to 4 and q is 0 to 4; said alkenyl and alkynyl R^{40} groups not containing -OH, -SH or $-N(R^{10})_2$ on a carbon containing a double or triple bond respectively; or

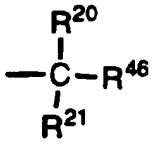
R^{40} represents phenyl substituted with a group selected from $-SO_2NH_2$, $-NHSO_2CH_3$, $-SO_2NHCH_3$, $-SO_2CH_3$, $-SOCH_3$, $-SCH_3$, or $-NHSO_2CF_3$, preferably, said group is located in the para position of the phenyl ring; or

R^{40} represents a group selected from

, or ;

R^{42} represents



wherein R^{20}, R^{21} and R^{46} are each independently selected from the group consisting of:

(1) H;

(2) $-(CH_2)_qSC(O)CH_3$ wherein q is 1 to 3;

(3) $-(CH_2)_qOSO_2CH_3$ wherein q is 1 to 3;

(4) -OH;

(5) $-CS(CH_2)_w$(substituted phenyl) wherein w is 1 to 3 and the substitutents on said substituted phenyl group are the same substitutents as described below for said substituted phenyl;

(6) $-NH_2$;

(7) -NHCBZ;

(8) $-NHC(O)OR^{22}$ wherein R^{22} is an alkyl group having from 1 to 5 carbon atoms, or R^{22} represents phenyl substituted with 1 to 3 alkyl groups;

(9) alkyl;

(10) $-(CH_2)_k$phenyl wherein k is 1 to 6;

(11) phenyl;

(12) substituted phenyl wherein the substituents are selected from the group consisting of: halo, NO_2, -OH, $-OCH_3$, $-NH_2$, $-NHR^{22}$, $-N(R^{22})_2$, alkyl, $-O(CH_2)_t$phenyl (wherein t is from 1 to 3), and $-O(CH_2)_t$substituted phenyl (wherein t is from 1 to 3);

(13) naphthyl;

(14) substituted naphthyl, wherein the substituents are as defined for substituted phenyl above;

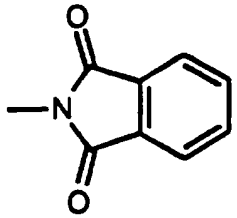
(15) bridged polycyclic hydrocarbons having from 5 to 10 carbon atoms;

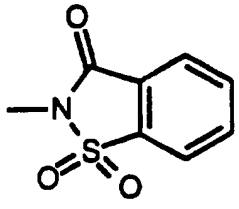
(16) cycloalkyl having from 5 to 7 carbon atoms;

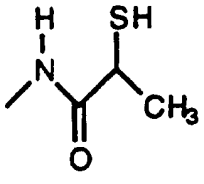
(17) heteroaryl;

(18) hydroxyalkyl;

(19) substituted pyridyl or substituted pyridyl N-oxide wherein the substituents are selected from methylpyridyl, morpholinyl, imidazolyl, 1-piperidinyl, 1-(4-methylpiperazinyl), $-S(O)_tR^{11}$, or any of the substituents given above for said substituted phenyl, and said substitutents are bound to a ring carbon by replacement of the hydrogen bound to said carbon;

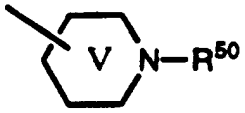
(20)  ;

(21)  ;

(22)  ;

(23) $-NHC(O)-(CH_2)_k$-phenyl or $-NH(O)-(CH_2)_k$-substitued phenyl, wherein said k is as defined above;

(24) piperidine Ring V:

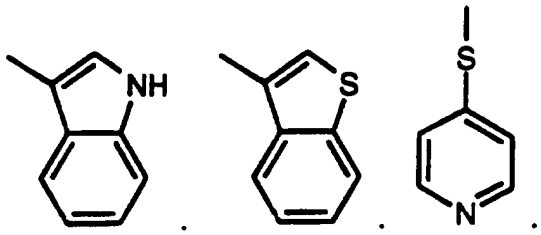


wherein R^{50} represents H, alkyl, alkylcarbonyl, alkyloxycarbonyl, haloalkyl, or -C(O)NH(R^{10}) wherein R^{10} is H or alkyl;

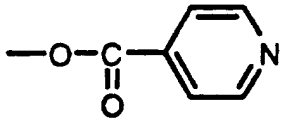
(25) -NHC(O)$CH_2C_6H_5$ or -NHC(O)CH_2-substituted-C_6H_5;

(26) -NHC(O)OC_6H_5;

(27) (28) (29)



(30) -OC(O)-heteroaryl, for example



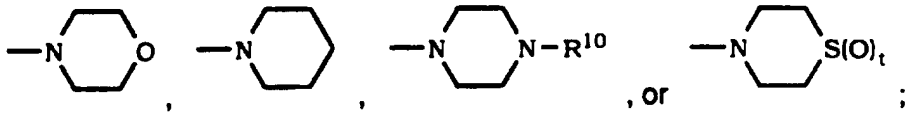
;

(31) -O-alkyl (e.g., -OCH_3); and

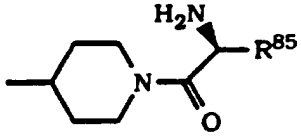
(32) -CF_3;

(33) -CN;

(34) a heterocycloalkyl group of the formula



(35) a piperidinyl group of the formula

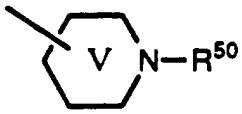


wherein R^{85} is H, alkyl, or alkyl substituted by -OH, -SCH_3 or -SH; and

(36) triazolyl; or

R^{20} and R^{21} taken together form a =O group and the remaining R^{46} is as defined above; or

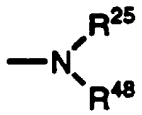
two of R^{20}, R^{21} and R^{46} taken together form piperidine Ring V



wherein R^{50} is as defined above;

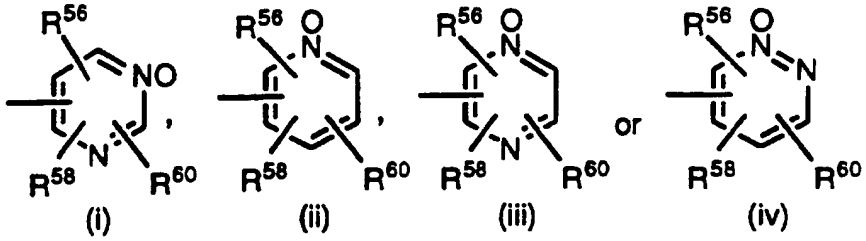
with the proviso that R^{46}, R^{20} and R^{21} are selected such that the carbon atom to which they are bound does not contain more than one heteroatom;

R^{44} represents



wherein R^{25} represents heteroaryl, N-methylpiperdinyl or aryl; and R^{48} represents H or alkyl;

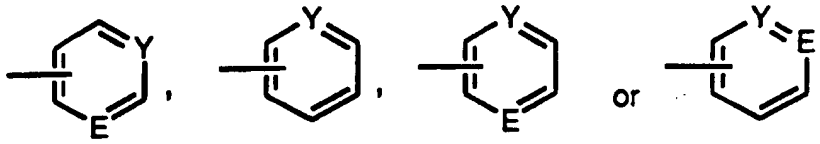
R^{54} represents an N-oxide heterocyclic group of the formula (i), (ii), (iii) or (iv):



(i) (ii) (iii) (iv)

wherein R^{56}, R^{58}, and R^{60} are the same or different and each is independently selected from H, halo, $-CF_3$, $-OR^{10}$, $-C(O)R^{10}$, $-SR^{10}$, $-S(O)_eR^{11}$ (wherein e is 1 or 2), $-N(R^{10})_2$, $-NO_2$, $-CO_2R^{10}$, $-OCO_2R^{11}$, $-OCOR^{10}$, alkyl, aryl, alkenyl or alkynyl, which alkyl may be substituted with $-OR^{10}$, $-SR^{10}$ or $-N(R^{10})_2$ and which alkenyl may be substituted with OR^{11} or SR^{11}; or

R^{54} represents an N-oxide heterocyclic group of the formula (ia), (iia), (iiia) or (iva):



(ia) (iia) (iiia) (iva)

wherein Y represents N^+-O^- and E represents N; or

R^{54} represents an alkyl group substituted with one of said N-oxide heterocyclic groups (i), (ii), (iii), (iv), (ia), (iia), (iiia) or (iva); and

Z represents O or S such that R can be taken in combination with R^5, R^6, R^7 or R^8 as defined above, or R represents R^{40}, R^{42}, R^{44} or R^{54};

with the proviso that when:

(1) R^1, R^2, R^3 and R^4 are independently selected from H, halo, $-CF_3$, $-OR^{10}$, $-COR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$, $-N(R^{10})_2$, $-NO_2$, $-OC(O)R^{10}$,

$-CO_2R^{10}$, $-OCO_2R^{11}$, -CN, $-NR^{10}COOR^{11}$, $-SR^{11}C(O)OR^{11}$, $-SR^{11}N(R^{75})_2$, benzotriazol-1-yloxy, tetrazol-5-ylthio, substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl; or R^1 and R^2 are selected from H, halo, $-CF_3$, $-OR^{10}$, $-COR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$, $-N(R^{10})_2$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, -CN, $-NR^{10}COOR^{11}$, $-SR^{11}C(O)OR^{11}$, $-SR^{11}N(R^{75})_2$, benzotriazol-1-yloxy, tetrazol-5-ylthio, substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl, and R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring (Ring III); and

(2) the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent $-R^{10}$, halo, $-OR^{11}$, $-OCO_2R^{11}$ or $-OC(O)R^{10}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2, $-(OR^{11})_2$, H and halo, dihalo, alkyl and H, $(alkyl)_2$, -H and $-OC(O)R^{10}$, H and $-OR^{10}$, =O, aryl and H, $=NOR^{10}$ or $-O-(CH_2)_p-O-$ wherein p is 2, 3 or 4;

then R is selected from:

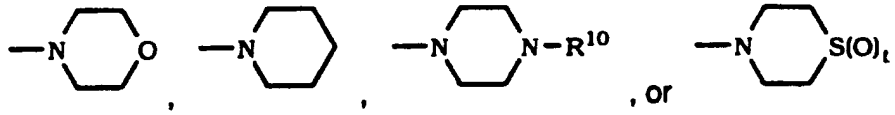
(a) R^{42} wherein at least one of R^{20}, R^{21} or R^{46} is selected from:

(1) substituted pyridyl or substituted pyridyl N-oxide wherein the substituents are selected from methylpyridyl, morpholinyl, imidazolyl, 1-piperidinyl, 1-(4-methylpiperazinyl), or $-S(O)_tR^{11}$;

(2) -CN;

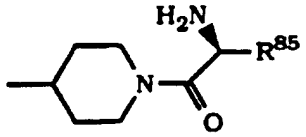
(3) triazolyl;

(4) a heterocycloalkyl group of the formula



; or

(5) a piperidinyl group of the formula

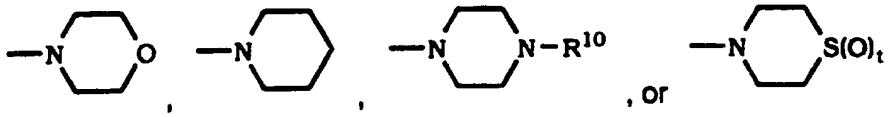


wherein R^{85} is H, alkyl, or alkyl substituted by -OH, $-SCH_3$ or -SH; or

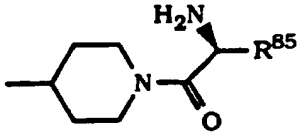
(b) R^{44} wherein R^{25} is N-methylpiperidinyl.

2. The method of Claim 1 wherein a is N and b, c, and d are carbon; R^1 and R^2 are the same or different and each is independently selected from H, halo, $-CF_3$, lower alkyl, or benzotriazol-1-yloxy, and R^1 is

at the C-4 position and R^2 is at the C-3 position; R^3 and R^4 are the same or different and each is independently selected from H or halo, and R^3 is at the C-8 position and R^4 is at the C-9 position; when the double bond between carbon atoms 5 and 6 is present, A and B independently represent H, lower alkyl or alkyloxy; and when the double bond between carbon atoms 5 and 6 is absent, A and B independently represent H_2, (-H and -OH) or =O; R^5, R^6, R^7, and R^8 are H; Z is O; and R represents R^{42} and the R^{46} is selected from: (1) -CN; triazolyl; (2) a heterocycloalkyl group of the formula

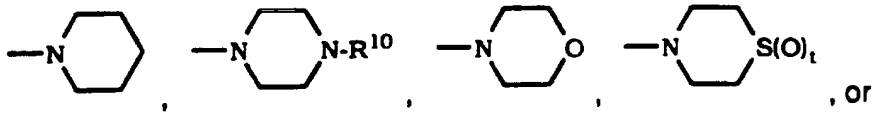


; (3) a piperidinyl group of the formula

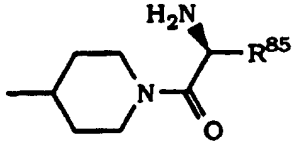


wherein R^{85} is H, alkyl, or alkyl substituted by -OH or $-SCH_3$; or (4) substituted pyridyl or substituted pyridyl N-oxide wherein the substituents are selected from methylpyridyl, morpholinyl, imidazolyl, 1-piperidinyl, 1-(4-methylpiperazinyl), or $-S(O)_tR^{11}$.

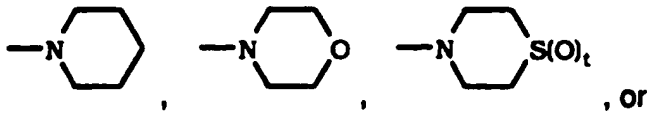
3. The method of Claim 2 wherein R^{20} and R^{21} are each independently selected from H and alkyl; R^3 is Cl; R^4 is H; R^1 and R^2 are individually selected from H, benzotriazol-1-yloxy, C_1 to C_4 alkyl or halo; and R^{46} represents triazolyl, a heterocycloalkyl of the formula



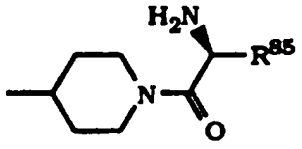
, or a piperidinyl group of the formula



4. The method of Claim 3 wherein both R^{20} and R^{21} are H, or both R^{20} and R^{21} are methyl; R^1 and R^2 are individually selected from H, Br, Cl, methyl or benzotriazol-1-yloxy; and R^{46} represents triazolyl, 1-N-methylpiperazinyl, 1-piperazinyl, a heterocycloalkyl of the formula



a piperidinyl group of the formula



5. The method of Claim 1 wherein a is N and b, c, and d are carbon; R^1 and R^2 are the same or different and each is independently selected from H, halo, $-CF_3$, lower alkyl, or benzotriazol-1-yloxy, and R^1 is at the C-4 position and R^2 is at the C-3 position; R^3 and R^4 are the same or different and each is independently selected from H or halo, and R^3 is at the C-8 position and R^4 is at the C-9 position; when the double bond between carbon atoms 5 and 6 is present, A and B independently represent H, lower alkyl or alkyloxy; and when the double bond between carbon atoms 5 and 6 is absent, A and B independently represent H_2, (-H and -OH) or =O; R^5, R^6, R^7, and R^8 are H; Z is O; and R represents R^{44} and the R^{25} represents, 3-N-methylpiperidinyl or 4-N-methylpiperidinyl.

6. The method of Claim 5 wherein R^3 is Cl; R^4 is H; R^{48} represents are H or methyl; and R^1 and R^2 are individually selected from H, benzotriazol-1-yloxy, methyl, Br or Cl.

7. The method of Claim 1 wherein the the cells inhibited are tumor cells expressing an activated ras oncogene.

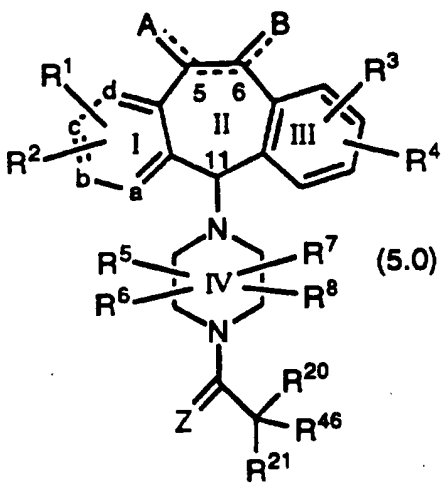
8. The method of Claim 7 wherein the cells inhibited are pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells or colon tumors cells.

9. The method of Claim 1 wherein the inhibition of the abnormal growth of cells occurs by the inhibition of farnesyl protein transferase.

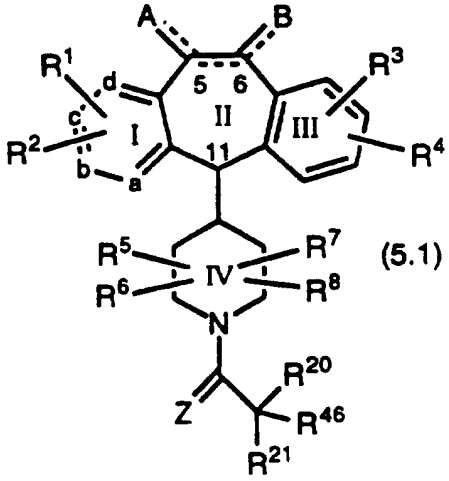
10. The method of Claim 1 wherein the inhibition is of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

11. The method of Claim 1 wherein the compound is selected from the compounds of Examples: 426, 400-G, 400-C, 400-F, 400-E, 425-H, 401, 400-B, 400, 400-L, 425-U, 413, 400-J, 417-B, 438, 411-W, 425-O, 400-D, 400-K, 410-G or 400-H.

12. A compound selected from a compound of the formula:



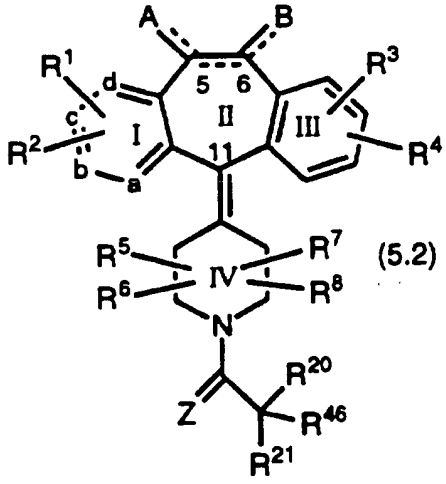
(5.0)



(5.1)

;

; or

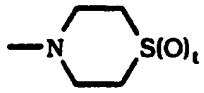


(5.2)

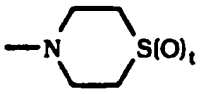
or a pharmaceutically acceptable salt or solvate thereof, wherein all the substituents are as defined in Claim 1.

13. The compound of Claim 12 wherein a is N and b, c, and d are carbon; R^1 and R^2 are the same or different and each is

independently selected from H, halo, $-CF_3$, lower alkyl, or benzotriazol-1-yloxy, and R^1 is at the C-4 position and R^2 is at the C-3 position; R^3 and R^4 are the same or different and each is independently selected from H or halo, and R^3 is at the C-8 position and R^4 is at the C-9 position; when the double bond between carbon atoms 5 and 6 is present, A and B independently represent H, lower alkyl or alkyloxy; and when the double bond between carbon atoms 5 and 6 is absent, A and B independently represent H_2, (-H and -OH) or =O; R^5, R^6, R^7, and R^8 are H; Z is O; and R^{46} is selected from triazolyl, 1-N-methylpiperazinyl, 1-piperazinyl or a heterocycloalkyl of the formula

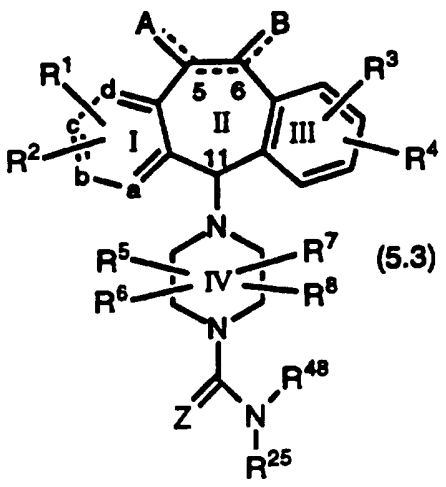


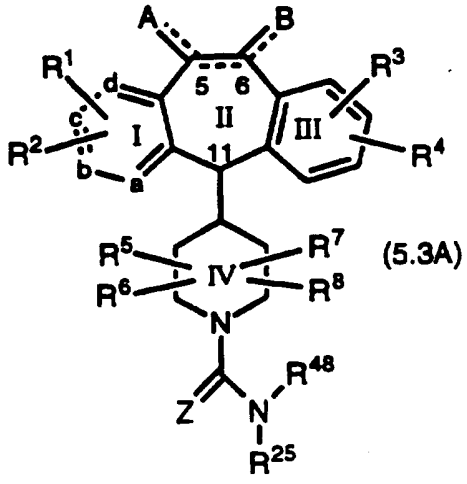
14. The compound of Claim 13 wherein R^{20} and R^{21} are each independently selected from H and alkyl; R^3 is Cl; R^4 is H; R^1 and R^2 are individually selected from H, benzotriazol-1-yloxy, C_1 to C_4 alkyl or halo; and R^{46} represents 1-N-methylpiperazinyl, 1-piperazinyl or a heterocycloalkyl of the formula



15. The compound of Claim 14 wherein both R^{20} and R^{21} are H, or both R^{20} and R^{21} are methyl; and R^1 and R^2 are individually selected from H, Br, Cl, methyl or benzotriazol-1-yloxy.

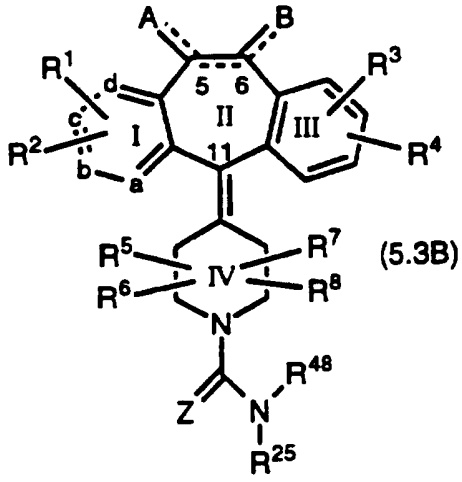
16. A compound selected from a compound of the formula:





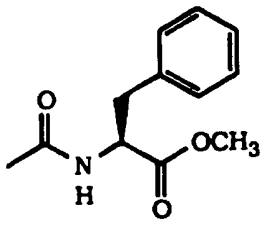
;

or



or a pharmaceutically acceptable salt thereof, wherein a, b, c, d, R^5, R^6, R^7, R^8, A, B and Z are as defined in Claim 1;

each R^1 and each R^2 is independently selected from H, halo, $-CF_3$, $-OR^{10}$, $-COR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$ (wherein t is 0, 1 or 2), -SCN, $-N(R^{10})_2$, $-NR^{10}R^{11}$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, -CN, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-CONHR^{10}$, $-CONHCH_2CH_2OH$, $-NR^{10}COOR^{11}$, $-SR^{11}C(O)OR^{11}$,



,

$-SR^{11}N(R^{75})_2$ (wherein each R^{75} is independently selected from H and $-C(O)OR^{11}$), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-

5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, $-OR^{10}$ or $-CO_2R^{10}$;

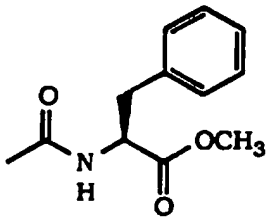
R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2, or R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring;

R^{25} represents heteroaryl, N-methylpiperidinyl or aryl; and

R^{48} represents H or alkyl; and

with the proviso that:

(1) when R^{25} is selected from heteroaryl or aryl then: (a) at least one of said R^1, R^2, R^3 and R^4 groups is selected from -SCN, $-NR^{10}R^{11}$, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-CONHR^{10}$, $-CONHCH_2CH_2OH$, or



; or

(b) the double bond between carbon atoms 5 and 6 is present and at least one of A and B represents $-NO_2$; and

(2) when R^{25} is N-methylpiperidinyl selected from 3-N-methyl-piperidinyl or 4-N-methylpiperidinyl then R^1 and R^2 are not H, halo, $-CF_3$, benzotriazol-1yloxy or lower alkyl when: (a) R^3 and R^4 are selected from H and halo; and (b) the double bond between carbon atoms 5 and 6 is present and A and B are selected from H, lower alkyl or lower alkoxy, or the double bond between carbon atoms 5 and 6 is absent and A and B are selected from H_2, (-H and -OH) or =O; and (c) R^5, R^6, R^7, and R^8 are H; and (d) Z is O.

17. A compound selected from a compound having the structure number: 5.200, 5.201, 5.202, 5.203, 5.204, 5.205, 5.206, 5.207, 5.208, 5.209, 5.210, 5.211, 5.212, 5.213, 5.214, 5.215, 5.216, 5.217, 5.218, 5.219, 5.220.

18. A compound selected from the compounds of Examples: 400-A, 400-M, 400-N, 400-P, 400-Q, 402, 402-A, 403, 404, 405, 406, 407, 410-H, 410-J, 410-L, 410-M, 410-Q, 410-R, 410-S, 410-T, 410-U, 410-V, 410-W, 410-X, 411, 411-A, 411-B, 411-C, 411-D, 411-E, 411-F, 411-G,

411-H, 411-J, 411-K, 411-L, 411-M, 411-N, 411-O, 411-P, 411-Q, 411-R, 411-S, 411-T, 411-U, 411-V, 411-X, 411-Z, 411-AA, 411-BB, 411-CC, 411-DD, 411-EE, 411-FF, 411-GG, 412, 412-A, 412-B, 412-C, 412-D, 412-E, 412-F, 412G, 412-H, 414, 414-A, 414-B, 415, 416, 417, 417-A, 418, 419, 420, 421, 422,422-A, 423, 423-A, 423-B, 424, 424-A, 425, 425-A, 425-B, 425-C, 425-D, 425-E, 425-F, 425-G, 425-J, 425-K, 425-L, 425-M, 425-N, 425-P, 425-Q, 425-R, 425-S, 425-T, 425-V, 426-A, 427, 427-A, 427-B, 427-C, 428, 428-A, 429, 430, 430-A, 431, 431-A, 431-B, 431-C, 431-D, 431-E, 431-F, 431-G, 432, 433, 433-A, 433-B, 433-C, 434, 434-A, 435, 436, 436-A, 436-B, 436-C, 436-D, 437, 438-A, 438-B, 439, 440, 440-A, 441, 500, 501, 502, 503, 504, 505, 506, 507 or 508.

19. A pharmaceutical composition for inhibiting the abnormal growth of cells comprising an effective amount of a compound of any of Claims 12, 16 or 18 in combination with a pharmaceutically acceptable carrier.

20. The use of a compound of any of Claims 12, 16 or 18 for the manufacture of a medicament for use in inhibiting the abnormal growth of cells.

21. The use of a compound of any of Claims 12, 16 or 18 for inhibiting the abnormal growth of cells.

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/US 96/03314

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/04 A61K31/445 C07D401/14 C07D401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 270 818 (SCHERING CORP) 15 June 1988 see claims	12-19
X	EP,A,0 396 083 (SCHERING CORP) 7 November 1990 see claims	12-19
A	WO,A,92 11034 (WELLCOME FOUND) 9 July 1992 cited in the application see the whole document	1-20
P,X	WO,A,95 10516 (SCHERING CORP) 20 April 1995 see claims	1-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
9 July 1996	17.07.96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/03314

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-11 and 21 are alineated to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte nal Application No
PCT/US 96/03314

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0270818	15-06-88	US-A-	4826853	02-05-89
		AT-T-	116310	15-01-95
		AU-B-	7285991	30-05-91
		AU-B-	604285	13-12-90
		AU-B-	8336287	25-05-88
		CA-A-	1305147	14-07-92
		CA-A-	1321589	24-08-93
		DE-D-	3750929	09-02-95
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		EP-A-	0330673	06-09-89
		EP-A-	0685476	06-12-95
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		DE-T-	69014393	01-06-95
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		KR-B-	9509859	29-08-95
		OA-A-	9521	15-11-92
		WO-A-	9013548	15-11-90
		US-A-	5151423	29-09-92
		US-A-	5438062	01-08-95
WO-A-9211034	09-07-92	AU-B-	665341	04-01-96
		AU-B-	9062691	22-07-92

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/US 96/03314

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9211034		CA-A-	2098198	18-06-92
		EP-A-	0563134	06-10-93
		JP-T-	6504772	02-06-94
		US-A-	5416091	16-05-95
WO-A-9510516	20-04-95	AU-B-	7970394	04-05-95